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ACUTE APPENDICITIS COMPLICATING THE ACUTE INFECTIOUS DISEASES OF CHILDHOOD*

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BOSTON

ACUTE appendicitis in children displays certain features in its pathology, clinical course, diagnosis and treatment, which vary considerably from those of the disease in adults. The development of appendicitis during the course of one of the acute infectious diseases or in a child exposed to them further complicates the problem.

It seems to be commonly accepted opinion that certain of the contagious diseases, such as measles, tend to be complicated by a higher than normal incidence of appendicitis, that the diagnosis of acute appendicitis is apt to be rendered more difficult or masked by the presence of one of these contagious diseases, and that the mortality and morbidity of acute appendicitis is higher when so complicated than that of appendicitis occurring alone.

Most reviews of the problem of appendicitis give little statistical consideration to these aspects. Ladd and Gross¹ mention an apparently increased frequency of acute appendicitis in children with measles. Babcock² also states that "infections that produce general lymphoid hyperplasia such as measles, scarlet fever — often precede appendicitis." Scott and Ware,³ on the other hand, in a more recent appraisal of appendicitis in children, believe that no causal connection exists between the acute contagions and other upper respiratory infections and acute appendicitis.

A check on the validity of these impressions was undertaken in a study of cases of acute appendicitis in children under twelve years of age seen during a twenty-one-year period, recently ended at the Haynes Memorial, the infectious disease unit of the Massachusetts Memorial Hospitals in Boston. This included a group of 100 consecutive cases in which the appendix was examined

demonstrated some stage of acute appendicitis. In 61 of these the appendix was perforated, and some degree of peritonitis existed. Although sufficient evidence of localization to warrant the use of the term "abscess" was noted in 17 cases, we have found this an unsatisfactory classification because in children appendiceal peritonitis tends to localize poorly. Clinically, they may well be far sicker than the term "appendiceal abscess" suggests when the condition is encountered in an adult, and often

TABLE 1 *Relation Between Type of Appendicitis and Mortality Rate*

TYPE	NO OF CASES	NO OF DEATHS	MORTALITY %
Acute (with no rupture)	35	1	2.8
Acute (with rupture and local or diffuse peritonitis)	61	7	11.5
Pinworms only	2	0	0
Normal appendix	2	0	0
Totals	100	8	
Average			8.0

require as vigorous and prompt treatment as cases without any tendency to localization of the peritonitis. Scott and Ware³ recognized this situation in classifying acute appendicitis at the Children's Hospital in Boston and grouped their cases as "acute, unruptured" and "acute, ruptured with local or diffuse peritonitis." In more than 1300 cases reported by them, perforation of the appendix had occurred in 44.8 per cent, as compared with 64 per cent in our series.

Only 4 cases of the 100 in this group revealed no acute inflammation on microscopical examination. Pinworm infestation was the only finding in 2 of these cases, although the symptomatology and physical findings were those of acute appendicitis. In the remaining 2 cases entirely negative pathological findings indicated errors in the clinical diagnoses.

PATHOLOGICAL FINDINGS

The pathologic changes found in these cases are listed in Table 1. Ninety-six patients (96 per cent)

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ASSOCIATION OF INFECTIOUS DISEASES WITH APPENDICITIS

Table 2 shows the distribution of the various infectious diseases associated with acute appendicitis in this series.

Eighty-eight of these children actually had an infectious disease and the remaining 12 had been exposed to or were thought to be in the prodromal stage of one at the time of admission. The three largest and nearly equivalent groups of cases of appendicitis correspond to the three most common diseases: scarlet fever, measles and chicken pox, which accounted for 77 of the 88 actual cases of infectious disease in this series. In Table 2 are listed also the admission totals for the various contagions at the Haynes Memorial over the twenty-one-year

TABLE 2. Twenty-One Year Experience with Appendicitis in 104 Cases (Children under Twelve Years)

DISEASE	CASES OF APPENDICITIS (HAYNES MEMORIAL)	TOTAL CASES OF INFECTIOUS DISEASE	
		ALL IN HAYNES MEMORIAL	IN ACUTE APPENDICITIS
Scarlet fever	2	12,192*	231
Measles	2	11,451*	84
Chicken pox	50	60	254
Pertussis	11	50	11
Rubella	—	—	—
Mumps	—	104	177
Miscellaneous	4	—	—
Total	104	—	—

*This figure represents 5 per cent of all reported cases of scarlet fever in Massachusetts.

†These children, although exposed, failed to develop a clinical case of disease. Four children had two of the common infectious diseases.

period 1927 to 1948. The experience with scarlet fever is revealed as much greater than that with any other disease because it has been the policy of the Massachusetts Department of Public Health to encourage routine hospitalization of all patients with scarlet fever whenever possible.

The 23 cases of appendicitis occurring in the large group of 12,192 patients with scarlet fever admitted to the hospital represented an incidence of only 0.2 per cent, which was probably a fair sample of the statewide experience. It is interesting to note that the approximate incidence of appendicitis in all children under the age of ten years calculated from mortality tables for the year 1947 in Massachusetts was also 0.2 per cent.*

Total admission figures for measles, chicken pox, pertussis and mumps at the Haynes Memorial are seen as relatively small compared with the total reported cases for the state (data supplied by the Massachusetts Department of Public Health) since admissions for these diseases were chiefly because

of complications. Similar incidence rates for appendicitis occurring in these diseases, therefore, cannot be calculated on any sound statistical basis, although it seems apparent from a study of Table 1 that such rates would probably be no higher than those for appendicitis in scarlet fever.

Our interpretation of these data is that, contrary to traditional opinion, children with scarlet fever and other common contagious diseases show no greater tendency to the development of acute appendicitis than otherwise normal children do.

INCIDENCE OF INFECTIOUS DISEASES ON DIAGNOSTIC ACCURACY

The diagnosis of acute appendicitis in a child already ill with an infectious disease may be a very difficult one to make, as every physician who faces this problem will testify. Statistically, the effect of such diseases on the accuracy with which co-existing appendicitis could be diagnosed prior to hospital admission probably is best reflected in certain data presented in Table 1. Sixty-one per cent of the acutely inflamed appendixes in our series were found to have ruptured, whereas only 44.8 per cent were ruptured in the Children's Hospital series. This higher incidence of rupture apparently cannot be attributed to a predominance of younger patients since only 41 per cent of the ruptured appendixes in our series were found in children under the age of six years, whereas the figure derived from the Children's Hospital series was 53 per cent. Further analysis of the data suggests also that our high percentage of perforation cannot be explained by a postulated acceleration of the appendiceal inflammation by the infectious disease. The average period of delay from onset of symptoms to hospitalization for simple acute appendicitis was 1.4 days, but for ruptured appendix with local or generalized peritonitis, it was 3.1 days. These delays are essentially the same as those encountered in children with appendicitis uncomplicated by such diseases, as comparison with figures derived from the large series at the Children's Hospital will reveal. Calculations from the data of Scott and Ware³ show average delays of 1.5 and 3.4 days for the corresponding stages of appendicitis. Undoubtedly, masking symptoms and signs such as abdominal pain, fever, nausea and vomiting and respiratory complaints, which are often part of the presenting picture of the acute contagion, have made the diagnostic problem more difficult for the referring doctors. The telltale signs of peritonitis, when these developed, usually could be distinguished readily enough from those of the contagion so that the delay in these cases after rupture was not of unusual duration. Five children, however, all with ruptured appendixes, were referred to the hospital without any suggestion of this diagnosis but merely because the courses of their infectious diseases seemed unfavorable.

*This calculation is based on an assumed mortality rate of approximately 5 per cent for acute appendicitis in this age group.

After admission to the hospital diagnosis was made earlier, of course, by more elaborate facilities, in addition to the fact that in most cases, signs were better established. It is not surprising, then, that a diagnosis of acute appendicitis leading to early operation could be made promptly after admission by the resident staff and consultants in 84 of 100 cases. In an additional case, operation was deliberately delayed for eighteen hours in an attempt to improve the condition of the critically ill and toxic child. Operation was delayed for twelve hours or more in 14 children because of uncertainties in diagnosis, but in only 9 of these was a sufficiently serious appendicitis found to have made this delay of any hazard to the patient. The entire series included only 1 case in which death resulted after continued failure to diagnose a ruptured appendix clinically in the hospital. These statistics, however, fail to indicate adequately the very real difficulty encountered occasionally at the Haynes Memorial in making the diagnosis of appendiceal peritonitis in very young children.

An undetermined number of children, possibly 50 or more, were admitted during the same period covered by this study with a question of acute appendicitis that could not be confirmed by further observation and study at the hospital. Lymphadenitis or lymphoid hyperplasia, acute enteritis, mumps oophoritis, pancreatitis, referred pain and even constipation were variously thought to account for the clinical pictures simulating appendicitis in these cases.

CASES WITH DELAY IN HOSPITAL DIAGNOSIS

As noted above, in 9 children with established and serious appendicitis, operation was delayed more than twelve hours from time of admission owing to difficulties in diagnosis. In 1 of these, which resulted in death, there was a probable delay of four days after the onset of appendicitis in a child who was convalescing in the hospital from scarlet fever. When actual pain and tenderness developed, operation was performed immediately, and a small abscess was encountered. The child did well initially but died thirty days later from meningitis and septicemia, which did not seem to bear any direct relation to the appendicitis. Ruptured appendixes and varying degrees of peritonitis were found in half (4 cases) of the other 8 patients in this group. Five of these children had active chicken pox. None of this group of 8 died, however.

In summary, it seems fair to say that the diagnosis of acute appendicitis in the hospital was made somewhat more difficult by the coexistence of the infectious diseases. Serious delays in diagnosis occurred in 9 cases or about 10 per cent of the total, several patients being very sick children and difficult therapeutic problems. Fortunately, there was only 1 fatal case in this group. No data

are available for comparison on the percentage of diagnostic delay in children with appendicitis uncomplicated by other diseases although it must be appreciable.

ANALYSIS OF DEATHS

There were 8 deaths in the whole series of 100 cases. One of these, mentioned above, resulted from a diagnostic error. This occurred in C M, a three-year-old girl, who had been exposed to pertussis and who entered the hospital on November 6, 1937,

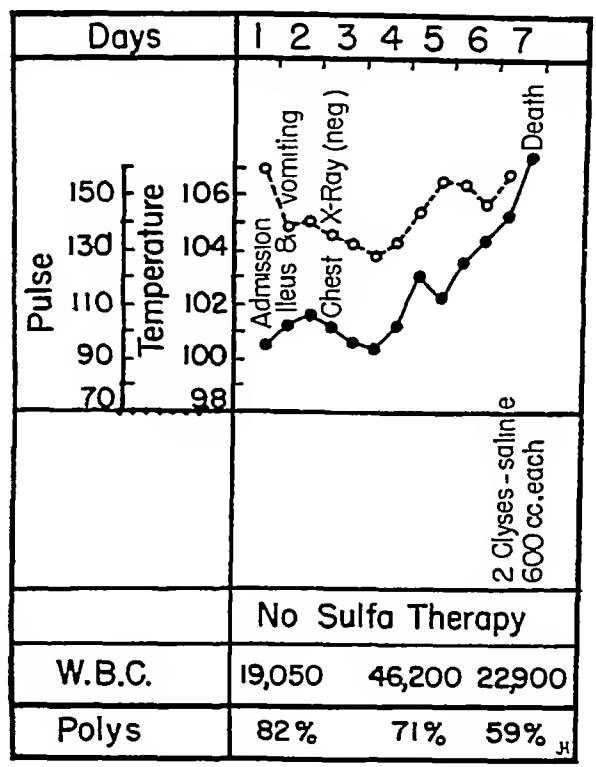


FIGURE 1. Clinical Course in a Thirty-Four-Month-Old Girl with Undiagnosed Appendiceal Peritonitis

after forty-eight hours of fever and vomiting in a very toxic state with distended abdomen and clinical signs of pneumonia. Although she was observed carefully and seen by two surgical consultants, the clinical findings never seemed adequate to warrant a diagnosis of acute surgical condition of the abdomen (Fig 1). Conservative therapy, which did not include sulfonamides was ineffectual, and the child died on the seventh day after admission, autopsy revealed a ruptured appendix and generalized peritonitis but no pneumonia.

The other 7 deaths in this series came after operation. In 1 of these children (referred to above) death occurred on the seventy-eighth hospital day being due to a streptococcal meningitis following bilateral mastoiditis, this case, in all fairness, could be excluded from the deaths caused by appen-

diectis Five other children died after operation, apparently from peritonitis, including the child who was given conservative therapy eighteen hours before operation, in an effort to improve his general condition. It seems significant that all 5 of these patients were treated in the years prior to so-called "modern therapy" when adequate fluids and electrolytes were not administered parenterally, stomach and intestinal intubation was not employed, and there was no chemotherapy. The descriptions of these cases were those of intractable ileus, dehydration and toxieity. Only 1 child among the 7 dying postoperatively was seen recently enough for modern supplementary therapy. In this patient, a girl with rubella, an appendectomy was performed for acute appendicitis without perforation, but an intractable ileus and hyperpyrexia developed postoperatively. She failed to respond to parenteral administration of fluids, sulfonamide therapy and gastric intubation, and although no autopsy was obtained, it was postulated that there might have been a "blow-out" of the appendiceal stump postoperatively or some other accidental cause of peritonitis.

CLINICAL OBSERVATIONS

Diagnosis

Of the several symptoms that suggested acute appendicitis in children, *pain* was the most obvious and the presenting symptom in 78 per cent. This was a right-sided or right-lower-quadrant pain in most cases. An initial periumbilical or epigastric pain was complained of less often than in adult patients. Other symptoms such as vomiting, fever and changes in bowel habits were reported frequently, but are such common symptoms of scarlet fever, measles and pertussis that they seemed to have no specific value in the differential diagnosis.

Certain physical signs seem to have been even more helpful than the history of pain in our series. *Local tenderness* over the area of the appendix was observed in the majority of children with acute appendicitis. *Spasm* was an informative sign at times in older children but rarely in very young children, probably because of voluntary splinting, crying and poor co-operation in general. We have listened carefully for intestinal peristalsis in recent years, and this has proved quite helpful at times in differentiating acute appendicitis from acute enteritis. Peristalsis was usually normal or diminished to auscultation in appendicitis, but almost invariably hyperactive in acute enteritis. The production of pain by coughing and rebound tenderness, probably explainable as resulting from the agitation of inflamed peritoneal surfaces, have been quite impressive and helpful diagnostically in some of the older children. Abdominal distention and ileus (in the absence of obvious reflex sources of this disturbance, such as pneumonia) was found

frequently in appendiceal peritonitis and was, in fact, suggestive of this diagnosis. Rectal examination has been of little help to us in the diagnosis of acute appendicitis except for the identification of a palpable mass in the pelvis. After one or more digital rectal examinations small children have become so apprehensive and poorly relaxed that it has been impossible to localize tenderness rectally.

The body temperature and the pulse rate have been influenced sufficiently by the contagious diseases present in many cases to be of little help in the diagnosis of the acute appendicitis.

The white-cell count and the differential count have also been confusing at times. In several cases of acute appendicitis developing in children with measles, for example, low total white-cell counts with mild neutropenia were found.

DISCUSSION

Surgical Management

It seems generally agreed that the diagnosis of acute appendicitis without perforation in a child, as well as in an adult, calls for early operation. This should never be so rushed, however, that sufficient time is not taken to restore disturbed fluid and chemical balances and to place the child on stomach drainage if there has been vomiting or evidence of ileus. Scott and Ware² and others^{1, 4, 5} emphasize the need of this preparation. The co-existence of one of the infectious diseases does not alter this indication for early surgery in our experience, except that the child may require a little longer preoperative preparation because of exposure to a longer period of toxieity and dehydration.

The time of operation is undoubtedly a more debatable question in cases of ruptured appendix with peritonitis. Conservative management of appendiceal peritonitis has proved valuable in many adult cases in the past, although undoubtedly the utilization of the more modern methods of treatment, particularly antibacterial therapy, must be altering the picture a great deal, permitting earlier surgery. We believe that continued conservative treatment of appendiceal peritonitis rarely is indicated in children—a belief based on personal experience as well as the testimony of several others.^{1, 3, 4}

For various reasons localization of the peritonitis cannot be relied on as effectively in children as in many adults. Anatomically, children do not have a sufficiently developed omentum and other peritoneal appendages available to aid in localization of a peritonitis. In addition, the appendix itself is far larger and longer in relation to the intestines and peritoneal structures than that in the adult, and the cecum often seems more mobile, creating greater potentialities of contamination by repeated leakage of pus and bowel content from a perforated appendix.

From a therapeutic point of view small children seriously ill with appendiceal peritonitis may be very difficult to handle. Fluid and electrolyte depletions develop rapidly. The veins are difficult to find and to keep cannulated for the necessary administration of replacement fluids. It is difficult to keep gastrointestinal tubes down and properly functioning.

A recent case illustrates the failure of conservative handling of appendiceal peritonitis despite all modern therapeutic efforts.

R. McA, a 2-year-old boy, was admitted to the Haynes Memorial Hospital in September, 1947, with a diagnosis of poliomyelitis, which was confirmed by spinal-fluid findings and clinical observations. For the first 2 days in the hospital his course was approximately that of other patients being treated at the same time. He had only a slight fever and little toxicity but presented a partial paralysis of the trunk and extremities. Two days after admission abdominal distention, with a quiet abdomen and some temperature and pulse rise, developed. Physical and x-ray signs of bronchopneumonia were present. He did not complain of specific abdominal pain, and there seemed to be no definite tenderness. The distention became more severe, and it was thought that he probably had the type of paralytic ileus not infrequently associated with pneumonia and sometimes with severe poliomyelitis. A Miller-Abbott tube was passed, adequate

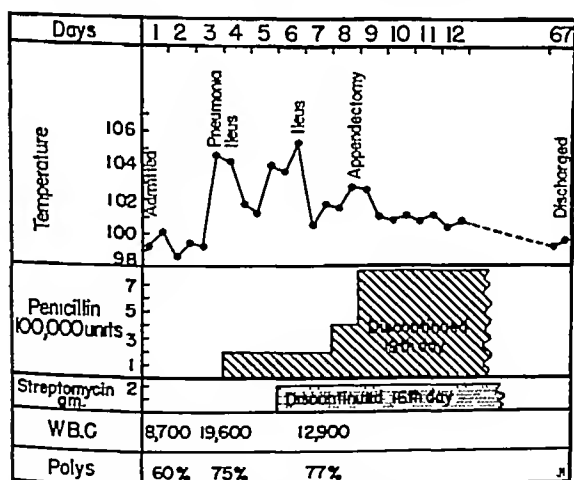


FIGURE 2 Clinical Course in a Two-Year-Old Boy with Poliomyelitis and Perforated Appendix

fluids administered parenterally and intramuscular injection of penicillin started. The patient improved somewhat but had a recurrence of distention in 24 hours and again became very toxic. On the 4th day after the onset of the original distention a mass could be felt in the right lower quadrant of the abdomen. He was seen in consultation by one of us (A. B. L.), and it was thought that he had peritonitis from a ruptured appendix, with partial localization. Operation was performed promptly through a small McBurney incision. A large collection of pus was drained from the upper portion of the pelvis and the right lower quadrant, and the poorly formed walls of the abscess cavity, formed largely by adjacent bowel, collapsed. The appendix lay directly beneath the incision and was removed very simply after ligation of its base. Only the abdominal wall superficial to the peritoneum was drained. Postoperatively, the child improved dramatically. The temperature fell to practically normal in less than a day, he had spontaneous bowel movements about 2 days postoperatively and improved rapidly from then on. The clinical course is demonstrated in Figure 2.

In this case dramatic improvement and recovery followed the drainage of the septic process and removal of the appendix, although until that time the patient was getting rapidly and steadily sicker despite heavy doses of penicillin and streptomycin, adequate fluids, transfusions, oxygen, gastrointestinal intubation and other supportive therapy.

It has been our general experience in cases of ruptured appendix with peritonitis in children that early removal of the appendix, as a source of continuing contamination, with aspiration of available pus, when supplemented by antibacterial and other appropriate therapy, almost always results in prompt improvement in the patient's condition and in recovery. Figure 3 shows the temperature chart

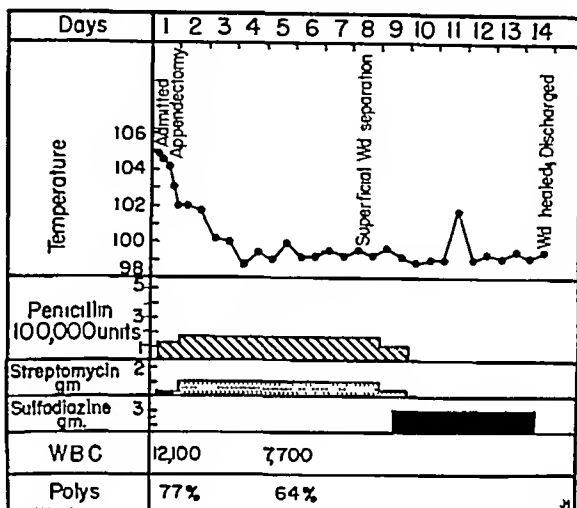


FIGURE 3 Clinical Course in a Six-Year-Old Boy with Chicken Pox and Appendiceal Peritonitis

and clinical data in J. N., a six-year-old boy, seen in July, 1947, whose course was typical of cases of this sort.

Anesthesia

Inhalation ether has been the preferred anesthetic, since this seemed easiest to administer to small children and probably the safest, yielding adequate relaxation when properly given. Spinal anesthesia has been used in a few older children.

Surgical Technique

The McBurney incision has been used almost exclusively in the past three years and has proved generally satisfactory in appendicitis in children, simply for removal of an acute appendix or when the condition is complicated by peritonitis or abscess. This incision has provided adequate access to the appendix without great disturbance of the intestines, and the spreading of contaminated material. It is interesting to note that when the type of incision was recorded for cases of perforated appendix in this series, 36 rectus incisions were

made with 1 case of extensive wound slough and 1 of serious wound infection, whereas there was only 1 deep wound infection in 21 McBurney incisions. In the infected McBurney incision the abdominal wall had not been drained despite contamination by intraperitoneal pus. It is only fair to say that most of the McBurney incisions were made during the era when chemotherapy was administered. We follow the practice of doubly ligating the base of the appendix and tying over it a portion of meso-appendix or any epiploic fat tab locally available and have had no proved case of leakage from the stump or other stump complications. We do not consider it necessary or desirable to drain the peritoneal cavity, except in the rare case in which it may not be possible to remove the appendix or to secure its base properly, or when a great deal of necrotic material in relation to an abscess is encountered. In the last three years covered by this study all children with appendiceal peritonitis, 12 in number, were treated in this way without intraperitoneal drains, and in no case was there any extension or failure of resolution of the peritonitis or any case of subsequent intraperitoneal abscess that, it seemed to us, might have been prevented by the use of a drain. Undoubtedly, the vigorous use of antibacterial drugs during this period has helped in the sterilization of the peritoneal exudate. There have been 2 cases of cul-de-sac cellulitis in this recent group, and both of these resolved completely under medical management. We have found it expedient to place a soft-rubber tissue drain down to the peritoneum in all cases of peritonitis. The peritoneal fatty tissue appears to be quite vulnerable to infection, and a deep abdominal-wall abscess with cellulitis is likely to originate in this area if this drainage is omitted.

Antibacterial-Drug Therapy

The sulfonamide drugs, penicillin and streptomycin undoubtedly have been valuable in assisting the localization of appendiceal peritonitis and the control of complications, such as pneumonia. In a group of 26 children with appendiceal peritonitis, prior to the advent of this treatment, there were 5 deaths, all due to sepsis, whereas in 21 recent cases, treated in the era of antibacterial drugs, only 1 death occurred. Sulfanilamide was the only form of chemotherapy available for administration to this particular patient. Although sulfanilamide was implanted intraperitoneally in several cases of this series, we now prefer to administer the sulfonamide drugs, when indicated, by the intravenous or oral

routes, believing that equivalent or better control of peritonitis can be obtained with greater safety. Much credit for the striking improvement under chemotherapy, however, must be given to the other aspects of modern supportive therapy in such sick surgical patients. Our present policy is to use heavy penicillin therapy by frequent intramuscular administrations supplemented by sulfadiazine or streptomycin in the more toxic children with peritonitis, particularly if the cultures demonstrate susceptible organisms.

SUMMARY AND CONCLUSIONS

An analysis of the experience with acute appendicitis at an active infectious-disease hospital indicates that there is no apparent predisposition to the development of acute appendicitis in children with the common infectious diseases.

The diagnosis of acute appendicitis was rendered somewhat more difficult by the coexistence of other diseases, but not to the point where any large number of diagnoses were missed or necessary surgical treatment postponed beyond the critical period.

A much higher incidence of ruptured appendix with peritonitis was found in this series (64 per cent) than in a group from a large children's clinic admitting very few patients with infectious disease (46 per cent). It seemed likely that this difference was due to greater difficulties in diagnosis during the period before admission to the hospital.

The mortality of 8 per cent in this series of 104 cases is high. In our opinion, it was attributable only in small part to diagnostic difficulties and the complications imposed by the coexistence of the infectious diseases. In the twenty-one-year period covered, 7 of the 8 deaths occurred before the use of modern treatment, including chemotherapy, parenteral administration of fluids, intubation and transfusions. These deaths were due to sepsis and might have been prevented had such therapy been available.

We are indebted to Dr. Louis Weinstein, physician and chief of service, Haynes Memorial Hospital, for his co-operation and helpful criticisms in the preparation of this paper.

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THE EVOLUTION OF INTERCAPILLARY GLOMERULOSCLEROSIS*

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BOSTON

IN 1936, Kimmelstiel and Wilson¹ described a diffuse, microscopic lesion in the kidneys of 8 middle-aged and elderly diabetic patients with hypertension, profuse albuminuria and generalized edema. The abnormality was termed "intercapillary glomerulosclerosis" and consisted of striking changes in the intercapillary tissue characterized by large hyaline masses confined to the centers of the glomeruli or glomerular lobules. Less severe degrees of this hyalinization were also reported. These observations have been confirmed and ex-

CASE REPORT

R S (B I H 30736), a 61-year-old married woman, had been told in 1935 by her family physician that her blood pressure was elevated. In March, 1936 she complained of loss of weight, weakness, pruritus vulvae, polyuria and polydipsia of 9 months' duration and of repeated attacks of gall-bladder colic without jaundice for 15 years. The blood pressure was 170/106. The urine gave a +++ test for sugar and contained no albumin. In April she was hospitalized for regulation of the diabetes mellitus. The left kidney was palpable; retrograde pyelography revealed a "large cyst in the lower pole." Intravenous cholecystography revealed no filling. The blood pressure was 166/100 and dropped to 110/70 during the rest of her hospital stay.

TABLE 1 Results of Urinalyses

DATE	NUMBER OF SPECIMENS EXAMINED	SPECIFIC GRAVITY	ALBUMIN	SUGAR	REMARKS
March 1936	2	1.008 and 1.018	0	0 and ---++	—
April and May 1936	11	1.008 to 1.010	0	0 to ---++	Hospitalization for cholecystectomy
September 1937 to March 1940	3	1.003	0	0 to +-+--	—
April 1940	2	1.010 and 1.012	0	0 to +	Hospitalization for nephrectomy
December 1940	3	1.006 to 1.012	0	0 to ---	Hospitalization for respiratory infection
June 1941	1	1.002	0	0	Hospitalization for bilateral saphenous-vein ligation
July and August 1941	9	1.002 to 1.026	— to +-	0 to +-+--	Hospitalization for sepsis
September 1941 to May 1942	14	1.002 to 1.016	0	0 to +	
July 1942 to November 1942	5	1.010 to 1.026	0	0 to —	—
December 1942	1	—	—	—	—
January 1943 to January 1944	8	1.008 to 1.020	++ to ---	0 to +	—
March 1944	1	1.018	++ to ++	—	—
April 1944	1	—	++ to ++	—	—
May 1944	1	—	++ to ++	—	—
August 1944	5	1.010 to 1.020	--- to +	0 to +	Hospitalization (terminal)

tended by many authors,^{2,5} and the subject has recently been reviewed by Kimmelstiel and Porter.⁹ The available published data are inconclusive concerning the period necessary for the evolution of the lesions of intercapillary glomerulosclerosis from their inception to the advanced stage. An opportunity was recently provided to study a patient who had had diabetes mellitus for the last eight years of her life. Four years before death a nephrectomy had been performed for a suspected neoplasm. Two years before death—that is six years after the onset of diabetes—massive albuminuria developed. Comparative histologic study of the surgically removed kidney and that obtained at autopsy provided a basis for elucidating the development of the renal disorder and the correlation of the latter with the clinical picture.

The diabetes was readily controlled with moderate doses of regular insulin. The urinary findings are recorded in Table 1. Cholecystectomy was performed and cholelithiasis and chronic cholecystitis were found. After discharge the patient did well on a diet and moderate doses of protamine zinc insulin. Repeated urine examinations revealed no albumin. In April 1940, because the left kidney had increased in size, a renal neoplasm was suspected and nephrectomy was performed. The diabetes remained well controlled. The blood pressure ranged between 110/70 and 150/80. Two urine examinations revealed no albumin. At operation a grape-fruit-sized renal cyst was found; the kidney without the cyst weighed 155 gm. The significant microscopic findings are listed in Table 2. Thereafter she again did well until December when she was readmitted for several days because of an upper respiratory infection. Three urine examinations revealed no albumin. An electrocardiogram was normal. The diabetes remained readily controlled with diet and small amounts of insulin. In February, 1941, for the first time she showed early bilateral lenticular opacities. The disks and vessels were normal; there were no hemorrhages or exudates. In June, 1941, bilateral high ligation of the saphenous veins was performed for varicose veins. The blood pressure was 160/86. Again, the urine was normal (Table 1). Three weeks postoperatively, after bleeding in the incision in the left groin, the patient experienced fever, chills and severe localized inflammation for which she was again hospitalized (Table 1). Chills and fever continued during the 1st week, and blood cultures revealed *Staphylococcus albus*. For the first time

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albuminuria was noted. After 5 days of oral and parenteral administration of sulfathiazole, the drug was omitted because of microscopical evidence of hematuria. On August 6, a large abscess in the left groin was incised and drained, the pus revealed *Staph. albus*. On August 8 perivascular abscesses of the left thigh and calf were drained, and the left greater saphenous vein was excised. She felt well until August 30, when chills, fever and tenderness in the left flank indicated sepsis. Sulfadiazine was administered for 1 month. Albuminuria had disappeared, and except for occasional microscopical evidence of hematuria and slight glycosuria the urine was normal. On September 8 an abscess in the posterior aspect of the left thigh was incised and drained, and 3 days later the left common iliac vein was ligated after a septic clot was found in the left external iliac vein. The septic course continued and bilateral necrosis of the heels and a decubitus ulcer of the sacrum developed. Sulfadiazine was again given for 2 weeks, during which albuminuria and

between the disk and macular region was a large, homogeneous, yellowish-white area of about 4 disk diameters over which the vessels were not seen. On May 13 further reduction in vision was found (4/200 on the right and 3/200 on the left).

After her discharge from the hospital in May, 1942, the diabetes was mild and insulin was unnecessary. Six months later massive albuminuria first appeared (Table 1). In June, 1944, she experienced pain in the left anterior portion of the chest. She was hospitalized on August 5 because of sudden onset of cough, dyspnea, fever, weakness, drowsiness, nausea and vomiting. Examination revealed fever, basal pulmonary rales and a blood pressure of 165/80. The elevated temperature subsided promptly after penicillin therapy. Glycosuria was readily controlled with 20 units of protamine zinc insulin daily. The blood nonprotein nitrogen fluctuated between 46 and 79 mg per 100 cc. The serum protein was 5.9 gm per 100 cc. An electrocardiogram revealed normal

TABLE 2 Microscopical Renal Findings

FINDING	LEFT KIDNEY REMOVED IN 1940*		RIGHT KIDNEY REMOVED AT AUTOPSY IN 1944†	
	PERCENTAGE OF GLOMERULI STUDIED	TOTALS	PERCENTAGE OF GLOMERULI STUDIED	TOTALS
Severe lesions of intercapillary glomerulosclerosis				
1 to 5 or more large (20 to 120 microns in diameter) discrete hyaline globular masses in addition to diffuse thickening of the axis of the glomerulus with or without small irregular hyaline masses				
5 or more large discrete hyaline globular masses per glomerulus	0 0		0 5	
4 discrete hyaline globular masses per glomerulus	0 0		2 0	
3 discrete hyaline globular masses per glomerulus	0 0		6 0	
2 discrete hyaline globular masses per glomerulus	0 0		17 0	
1 discrete hyaline globular mass per glomerulus	0 4‡	0 4	22 0	47 5
Moderately severe lesions of intercapillary glomerulosclerosis				
Small irregular hyaline masses in midst of diffuse thickening of axis of glomerulus	0 0	0 0	25 0	25 0
Mild lesions of intercapillary glomerulosclerosis				
Diffuse thickening of axis of glomerulus	0 0	0 0	15 0	15 0
Hyalinized (fibrosed) glomeruli	3 0	3 0	12 0	12 0
Normal glomeruli	96 6	96 6	0 5	0 5
		100 0		100 0
Hyalinization of afferent arterioles				
+++	0		6 0	
++	0		4 0	
+	7 0		7 0	
0	93 0	100 0	83 0	100 0
Capsular thickening				
+++	0		17 0	
++	5 0		7 0	
+	11 0		9 0	
0	84 0	100 0	67 0	100 0
Adhesions of glomerular tuft to capsule	4 0		9 0	
No adhesions	96 0	100 00	91 0	100 0

*252 glomeruli studied

†203 glomeruli studied

‡Not associated with axial thickening

hematuria were absent. After excision of the necrotic tissue over the sacrum the patient became afebrile, and the ulcers of the heels disappeared. On January 24, 1942, an abscess under the nail of the right great toe was drained and healed slowly. Bilateral foot drop developed, the knee jerks, ankle jerks and vibration sense were absent. Insulin was not necessary during the 10-month period of hospitalization. She was discharged on May 1, 1942.

She was checked at monthly intervals during the remainder of 1942, and occasionally thereafter. Her vision was 20/100 on the right and 20/40 on the left. The neurologic manifestations showed little improvement. The sacral lesion responded slowly but was not completely healed until September 21, 1943. Throughout this period, the blood pressure was approximately 160/90.

Gradually, her vision became impaired until on April 22, 1944, it was 8/200 on the right and 4/200 on the left. Numerous small lenticular and vitreous opacities were seen. Ophthalmoscopic examination revealed for the first time slight blurring of both disk margins and small hemorrhages intermingled with clump-like, white exudates of different sizes between the disks and macular regions in the left fundus

rhythm, with a rate of 65, ventricular premature beats, a small Q wave in Lead 3 and inverted T waves in Leads 2, 3 and 4. Lethargy, incontinence of urine and recurrence of sacral decubitus ulcers characterized the remainder of her hospital course, and she died on August 20.

Autopsy (A44-77), performed 4½ hours after death, showed minimal edema of the ankles. No fluid was present in the pleural or peritoneal cavities.

The heart weighed 340 gm. The coronary arteries were sclerotic. The left ventricular wall was 1.3 cm and the right 0.5 cm in thickness. At the anterior aspect of the apex of the left ventricle an area of soft myocardium was overlaid by a friable mural thrombus. Microscopical examination of the heart revealed patchy fibrosis throughout the myocardium and an organized endocardial thrombus overlying a completely healed infarct at the apex.

The pancreas was normal on gross examination and microscopically revealed occasional hyaline arteriolar change. The lungs showed patches of bronchopneumonia. The spleen was normal in size and weight and contained a small infarct. The liver and adrenal glands were normal on gross and microscopical examination. The duodenum ex-

hibited an old ulcer in the first portion. Gross and microscopical examination of the brain revealed moderate atheromatous changes of the arteries and focal areas of encephalomalacia. The aorta and external iliac arteries exhibited moderate atheromatous changes.

The remaining right kidney weighed 200 gm. On gross section, the cortex was pale and measured approximately 7.0 mm in thickness. The line of demarcation between the cortex and the medulla was poorly defined in contrast to the kidney removed 4 years previously, which, except for the cyst, had been essentially normal on gross examination.

Both kidneys were subjected to the same type of microscopical analysis. Sections from both organs stained with methyl-violet and iodine showed no amyloid; sections were also stained with hematoxylin and eosin, eosin and methylene blue and Mallory's aniline blue.

All the glomeruli in the available sections were individually studied. An attempt was made to evaluate the degree to which intercapillary thickening involved each glomerulus. The glomeruli that exhibited one to five or more large (20 to 120 microns in diameter), discrete hyaline globular masses in addition to diffuse thickening of the axis with or without small irregular hyaline masses were considered to have a severe degree of intercapillary glomerulosclerosis. The moderately severe lesions were those in which the glomeruli contained small irregular hyaline masses (less than 20 microns in diameter) in the midst of diffuse thickening of the axis of the glomerulus. The mild lesions consisted of only a diffuse thickening of the axis of the glomerulus. The extent of the involvement was evaluated by determination of the percentage of glomeruli exhibiting the lesions described above. The percentage showing complete hyalinization and that revealing afferent arteriolar hyalinization, capsular thickening and capsular adhesions were also calculated (Table 2).

OBSERVATIONS AND DISCUSSION

Of the 252 glomeruli studied in the sections of the kidney removed four years before death, 8 (3 per cent) were so completely hyalinized that little can be said concerning the mechanism of the fibrosis. The remaining 244 glomeruli showed nothing that could be interpreted as intercapillary hyaline thickening except for a single hyaline mass in the periphery of one glomerular lobule (Fig. 1). It is generally agreed that such masses are specific for the histologic picture in the kidney in diabetes mellitus if they are also associated with additional axial manifestations of hyaline thickening. It is noteworthy that this single glomerulus containing the hyaline mass showed no other thickening of the glomerular axis.

This isolated glomerular lesion may have represented the onset of intercapillary glomerulosclerosis. This is unlikely since it would be reasonable to expect that in the kidney obtained at autopsy, in which the fully developed picture of intercapillary glomerulosclerosis was seen, some glomeruli involved by a mild or early process should have been found simulating the isolated lesion discovered in the earlier specimen. As pointed out below, it is striking that none of the glomeruli seen at autopsy showed this picture, wherever discrete hyaline masses were found they were always associated with thickening of other parts of the glomerular axis. Accordingly, we believe that the single lesion described above bears no relation to the intercapillary glomerulosclerosis that developed later. It probably represents the reparative process con-

sequent to a variety of glomerular injuries not related to the diabetic state.

Of the 203 glomeruli studied in the kidney obtained at autopsy, 25 were so completely hyalinized that little can be said concerning the mechanism of the fibrosis. Only 1 glomerulus out of the remaining 178 was devoid of intercapillary thickening. Various degrees of this abnormality from severe to mild were found. Because of confusion in the literature regarding the various stages of this process,⁹ we consider it indispensable to grade the degree of renal involvement according to the extent of the



FIGURE 1 Section of Kidney Removed Four Years before Death. A glomerulus with a single intercapillary hyaline mass (hematoxylin and eosin stain $\times 450$).

process in each glomerulus and the percentage of glomeruli so affected (Table 2) as some authors have attempted.^{6,7} The lesions of severe degree were found in 47.5 per cent of the glomeruli (Fig. 2-4). An additional 40 per cent showed less severe lesions comprising moderately severe lesions in 25 per cent and mild lesions in 15 per cent.

The relatively high percentage of the severe lesions in the kidney removed at autopsy represents an advanced stage in the development of intercapillary glomerulosclerosis and is considered consistent with the diagnosis of diabetes mellitus. Allen¹⁰ has recently stated, "I am altogether convinced of the specificity of the nodular lesion," and

Bell⁷ considers this lesion almost pathognomonic for diabetes. The mild lesions are considered by some authors as the forerunner of the nodular type, but their relation to diabetes has not been established.⁹ The moderately severe lesions are believed

The positive correlation between the severity of the renal lesions of intercapillary glomerulosclerosis and the degree of albuminuria has been emphasized by Henderson et al.⁵ and others.^{7, 9} Our patient showed no albuminuria during the four years prior to nor during the fourteen months following the nephrectomy in April, 1940. In July and August, 1941, during the period of severe sepsis and sulfathiazole treatment, all urine examinations revealed + to ++ tests for albumin (Table 1). In spite of recurrent sepsis and sulfadiazine therapy from September to November, 1941, albuminuria was absent. Repeated urine examinations until December, 1942, showed no albumin. Appearance and disappearance of albuminuria are consistent with an acute inflammatory process that healed. The possibility that the transient albuminuria was due to intercapillary glomerulosclerosis is unlikely because in the latter condition the albuminuria is constant⁷ and continuous once it appears. Thus,



FIGURE 2 Section of Kidney Removed at Autopsy
A glomerulus with intercapillary hyaline thickening and two large discrete hyaline masses (hematoxylin and eosin stain $\times 450$)

to represent an intermediate stage in the development of the severe or nodular lesions.⁸

Other lesions such as afferent arteriolar hyalinization and glomerular capsular thickening and adhesions not generally considered an essential part of the picture of intercapillary glomerulosclerosis were present in the glomeruli of both kidneys. There was some increase in the incidence of these lesions in the four-year interval. Hyalinization of the afferent arterioles as seen in so-called benign nephrosclerosis increased from 7 to 17 per cent. The thickened glomerular capsules increased from 16 to 33 per cent. The incidence of adhesions of the glomerular tuft to the glomerular capsule, considered by many a concomitant of chronic glomerulonephritis, increased from 4 to 9 per cent. Because of the nonspecificity of hyalinized glomeruli their increase from 3 to 12 per cent cannot be considered of much help in evaluating the development of the lesions of intercapillary glomerulosclerosis.



FIGURE 3 Section of Kidney Removed at Autopsy
A glomerulus with intercapillary hyaline thickening and small irregular and large discrete hyaline masses (hematoxylin and eosin stain $\times 450$)

beginning in December, 1942, albuminuria recurred without any antecedent infection and continued in massive amounts until the patient died from renal insufficiency in August, 1944. In view of the large number of severe lesions of intercapillary glomerulo-

sclerosis found in the remaining kidney at autopsy, we believe that the correlation between these lesions and the massive continuous albuminuria is justifiable.

Intercapillary glomerulosclerosis, retinopathy and neuropathy are considered by many as degenerative concomitants of the diabetic state.⁵⁻¹⁰ Henderson et al⁵ called attention to the close relation between advanced diabetic retinopathy and the severe lesions of intercapillary glomerulosclerosis.

In our patient the clinical evidence for degenerative phenomena associated with diabetes developed as follows: diabetes mellitus was first discovered in 1936 and was readily controlled by dietary regulation and moderate or small doses of insulin until 1941, when she was hospitalized for severe sepsis after high ligation of the saphenous veins. From the beginning of the ten-month period of hospitalization insulin was unnecessary until the terminal illness in 1944. Peripheral neuropathy developed in 1942 and improved slightly during the remainder of her life. Impairment of vision, first noted in 1942, progressed gradually until serious reduction of vision associated with advanced diabetic retinopathy was found in 1944.

It is noteworthy that in spite of the excellent control of the diabetic state, neuropathy, retinopathy and massive albuminuria developed six years after the discovery of diabetes mellitus and persisted to the eighth year, when the patient died from renal insufficiency. This observation is similar to those of other authors,¹¹⁻¹² one of whom stated that "the duration of diabetes mellitus rather than the method of treatment is the most important factor in the development of the degenerative changes."¹⁰

At no time, however, did our patient present the nephrotic syndrome, and renal insufficiency supervened only in her terminal illness. In this connection it is noteworthy that intercapillary glomerulosclerosis of as severe degree as was found in this patient is not necessarily associated with the nephrotic syndrome originally observed in the cases described by Kimmelstiel and Wilson.¹ The development of the nephrotic syndrome may be related to the duration of the severe intercapillary lesions before renal insufficiency occurs.

Of fundamental importance is the demonstration that our patient showed no pathological evidence of intercapillary glomerulosclerosis at the time of the nephrectomy although she had been suffering from diabetes and mild hypertension for four years, and yet at some time during the next four years degenerative phenomena in the peripheral nerves and eyes and also massive albuminuria supervened. Clinical evidence of the pathologic renal process did not appear until two years before death, in the sixth year of the diabetes, and at autopsy the fully developed picture of severe intercapillary glomerulosclerosis in the remaining kidney was evident.

On the basis of clinical observation on 43 patients Mann et al¹³ reported that the average duration of life after the appearance of signs of renal disease was six and four-tenth years (range two to twelve years). Our patient's rapid course may have been due to sepsis or the fact that she had only one kidney when the degenerative phenomena associated with diabetes mellitus developed, or to both.

SUMMARY

A single kidney obtained at autopsy from a patient with diabetes mellitus of eight years' duration



FIGURE 4. Section of Kidney Removed at Autopsy. Two glomeruli with intercapillary thickening and multiple small irregular and large discrete hyaline masses (Fematoxylin and eosin stain $\times 300$).

showed severe intercapillary sclerosis in 47.5 per cent of the glomeruli. The other kidney, removed four years earlier for a suspected neoplasm, showed no evidence of intercapillary glomerulosclerosis.

Six years after the onset of diabetes mellitus, neuropathy, retinopathy and massive albuminuria developed and persisted until the eighth year, when the patient died from renal insufficiency. At no time was the nephrotic syndrome present.

The lesions of intercapillary glomerulosclerosis definitely developed during the last four years of life and possibly only during the last two years.

Bell⁷ considers this lesion almost pathognomonic for diabetes. The mild lesions are considered by some authors as the forerunner of the nodular type, but their relation to diabetes has not been established.⁹ The moderately severe lesions are believed



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FIGURE 3 Section of Kidney Removed at Autopsy.
A glomerulus with intercapillary hyaline thickening and small irregular and large discrete hyaline masses (hematoxylin and eosin stain $\times 450$)

beginning in December, 1942, albuminuria recurred without any antecedent infection and continued in massive amounts until the patient died from renal insufficiency in August, 1944. In view of the large number of severe lesions of intercapillary glomerulo-

MATERIALS AND METHODS

Three hundred consecutive urine tests submitted to the laboratory of the Mallory Institute of Pathology of the Boston City Hospital for the diagnosis of possible pregnancy comprise this report. These tests represent all the varieties of diagnostic problems that may be encountered in any general-hospital laboratory, and, so far as possible, all the samples are consecutive. Hence the present report should reflect common clinical experience. As in any general pregnancy diagnostic work, the urine specimens submitted for hormonal assay fell into one of several fairly well defined clinical categories. For the most part these can be stated as possible normal pregnancy, possible ectopic pregnancy, possible fetal death or miscarriage, in which the problem of evaluating the viability of the gestation hinges on the hormone level in the urine, and a pelvic mass in which the differential diagnosis lies between intra-abdominal tumor and pregnancy or both. Almost all the 300 tests fell into one of these four groups. A few tests were performed after surgical removal of hydatidiform moles. Since each of these categories presents a somewhat different laboratory diagnostic problem, it seems advisable to study each group separately. Thus the performance of the frog test can be specifically evaluated in each category, undistorted by the good or bad results obtained in the others.

In each case the validity of the laboratory diagnosis was checked by a clinical follow-up study of the patient, for such time as was required to make certain the clinical status of the patient. In normal pregnancies, a clinical follow-up period of a few months usually sufficed. In the urine samples submitted from patients suspected of miscarrying, the exact status of the pregnancy at the time of performance of the test was frequently very difficult to ascertain. Many such tests were therefore discarded as being insufficiently clearcut from the clinical standpoint for inclusion. When possible, histologic study of curettage or surgical specimens was used to corroborate the clinical diagnosis. In a few cases parallel injections with rats or rabbits were employed as controls for the frog test. Whatever the method, in each test cited in the present series a careful evaluation of the validity of the test was finally achieved.

The technic for performance of the test is substantially identical with that reported in an earlier paper and is therefore described only briefly.⁵ In essence, it consists in the injection of 5 cc of first-morning urine into the dorsal lymph sac of adult male frogs. No preliminary treatment of the urine is required except for occasional crude filtration of grossly turbid specimens. Approximately half an hour after the injection microscopical examination of the cloacal fluid for sperm is begun, the hanging-drop technic being used. The reaction of the

individual animal is followed for approximately two hours unless a positive reaction occurs earlier. As indicated before, to the best of our knowledge, no reaction ever begins after a two-hour interval. In general, positive reactions begin in thirty to forty-five minutes and persist for several hours, and in general they represent "all-or-none" responses. Rarely, an animal reacts with the release of only a few sperm. Our experience indicates that in a positive reaction many sperm may be found in any high-power field. The basis for so-called weakly positive reactions is obscure, but it is clear that they bear no apparent relation to the original titer of hormone injected, probably representing variations in the reactivity of the individual frog. All tests have been performed on adult male frogs run in pairs, the animals being obtained from local collectors. However, since the animals used are captured in the wild state and since estimation of age, to say nothing of sex, is difficult, it would be wise when possible to use 3 animals per test, simply to lower the mathematical probability of encountering all immature or superannuated animals on any given specimen of urine. Although this difficulty in selecting suitable animals may be of some theoretic significance, practically speaking our results indicate that it has not offered any real problem. For similar reasons it is probably good practice to open all "negative test" frogs simply to ascertain by inspection of the gonads that the animals used are male, the external features being insufficiently characteristic for most workers to separate definitely males from females.

RESULTS

The results are presented and discussed under each of four headings cited above.

Possible Pregnancy

As mentioned earlier this category is meant to include patients who present themselves to the physician as possibly pregnant with a history of a missed menstrual period or some disturbance in the regularity of the menstrual cycle. A total of 242 urine tests fall into this group, with the following results: correct positive, 113, correct negative, 117, false positive, 1, and false negative, 11.

With relation to the correct-positive reactions, it is obvious that these tests merely indicate the presence of an apparently uncomplicated early pregnancy. It is well known that at the beginning of pregnancy the titers of gonadotropin are extremely low and only begin to rise to any appreciable level after approximately fifteen days of gestation. Since many urine samples are submitted for analysis after only one or two days of amenorrhea, some even before the first missed period, it did not seem justifiable to call these extremely early negative tests false negative. It was arbitrarily decided, therefore, that fifteen days after the first missed period was

when the degenerative phenomena and massive albuminuria mentioned above were found

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THE RELIABILITY OF THE MALE NORTH AMERICAN FROG (*RANA PIPIENS*) IN THE DIAGNOSIS OF PREGNANCY*

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WITHIN the past two years many reports summarized by Galli-Mainini¹ have appeared describing a new technic for diagnosis of pregnancy utilizing male amphibia. A great many species of frogs and toads have been described as useful for this procedure, and it is highly probable that many varieties of amphibia have equal value. At the present time two species have received the greatest attention. Galli-Mainini,² working in South America, has used a toad indigenous to that area—the *Bufo arenarum*. His recent report on the results of approximately 1000 tests using this amphibian indicates a high degree of accuracy, approximately 98 per cent, with no false-positive results, the 2 per cent errors being false-negative reactions. In the United States a widely indigenous frog, the common leopard frog known as the *Rana pipiens*, has been used for this work, chiefly by Wiltberger and Miller,^{3, 4} and Robbins and Parker.⁵ To date reports from these North American sources have been of a provisional type, and no extended clinical trial has yet been cited. The advantages of the use of male amphibia are so striking that the technic has created wide interest and possibly considerable use. It therefore seems both necessary and urgent to report results obtained to date with the use of the male frog. Only thus can it be determined whether the test is of sufficient sensitivity and specificity to merit further use.

The practical advantages of this technic are so striking that only a lack of accuracy could block its widespread adoption. In contrast to the five days required for the performance of an Aschheim-Zondek test on immature rats or the two days re-

quired by the female rabbit in the Friedman modification, the male-frog test requires at the most two hours.

The cost of male frogs is only a small fraction of that of rats or rabbits, and, moreover, the amphibia can be kept in small aquaria. From the standpoint of economy and ease in maintenance of a stock of available animals, the frogs are therefore vastly superior to these mammalia.

The only significant problem encountered to date in the use of these amphibia has been alluded to in an earlier report⁶—namely, the toxicity of many urines for them. At the time of the previous writing,⁶ death of the frogs subsequent to their injection with 5 cc of whole urine was a frequent occurrence. For totally obscure reasons, this problem has become much less bothersome at the present time, being no more common with male frogs than with other types of laboratory assay animals. However, it was because of this toxicity of urine that blood serum, containing fewer waste metabolites than urine, was suggested as a method of circumventing the problem.⁶ Accordingly, 5 cc of blood serum was substituted for urine in the performance of the test. Although on purely theoretic grounds serum should contain an adequate source of gonadotropic hormones during pregnancy, and although serum has been successfully substituted for urine in the performance of the Friedman test as well as others, it soon became apparent that serum was quite unsatisfactory for the *Rana pipiens* test. In a fairly large number of patients studied, proved subsequently to be pregnant, serum gave many false-negative results—about 15 to 20 per cent of the total series.⁷ As a consequence, the substitution of serum in the performance of this technic has been dropped, and the present communication concerns itself only with an analysis of the results of the use of urine.

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MATERIALS AND METHODS

Three hundred consecutive urine tests submitted to the laboratory of the Mallory Institute of Pathology of the Boston City Hospital for the diagnosis of possible pregnancy comprise this report. These tests represent all the varieties of diagnostic problems that may be encountered in any general-hospital laboratory, and, so far as possible, all the samples are consecutive. Hence the present report should reflect common clinical experience. As in any general pregnancy diagnostic work, the urine specimens submitted for hormonal assay fell into one of several fairly well defined clinical categories. For the most part these can be stated as possible normal pregnancy, possible ectopic pregnancy, possible fetal death or miscarriage, in which the problem of evaluating the viability of the gestation hinges on the hormone level in the urine, and a pelvic mass in which the differential diagnosis lies between intra-abdominal tumor and pregnancy or both. Almost all the 300 tests fell into one of these four groups. A few tests were performed after surgical removal of hydatidiform moles. Since each of these categories presents a somewhat different laboratory diagnostic problem, it seems advisable to study each group separately. Thus the performance of the frog test can be specifically evaluated in each category, undistorted by the good or bad results obtained in the others.

In each case the validity of the laboratory diagnosis was checked by a clinical follow-up study of the patient, for such time as was required to make certain the clinical status of the patient. In normal pregnancies, a clinical follow-up period of a few months usually sufficed. In the urine samples submitted from patients suspected of miscarriage, the exact status of the pregnancy at the time of performance of the test was frequently very difficult to ascertain. Many such tests were therefore discarded as being insufficiently clearcut from the clinical standpoint for inclusion. When possible, histologic study of curettage or surgical specimens was used to corroborate the clinical diagnosis. In a few cases parallel injections with rats or rabbits were employed as controls for the frog test. Whatever the method, in each test cited in the present series a careful evaluation of the validity of the test was finally achieved.

The technic for performance of the test is substantially identical with that reported in an earlier paper and is therefore described only briefly.⁵ In essence, it consists in the injection of 5 cc of first-morning urine into the dorsal lymph sac of adult male frogs. No preliminary treatment of the urine is required except for occasional crude filtration of grossly turbid specimens. Approximately half an hour after the injection microscopical examination of the cloacal fluid for sperm is begun, the hanging-drop technic being used. The reaction of the

individual animal is followed for approximately two hours unless a positive reaction occurs earlier. As indicated before, to the best of our knowledge, no reaction ever begins after a two-hour interval. In general, positive reactions begin in thirty to forty-five minutes and persist for several hours, and in general they represent "all-or-none" responses. Rarely, an animal reacts with the release of only a few sperm. Our experience indicates that in a positive reaction many sperm may be found in any high-power field. The basis for so-called weakly positive reactions is obscure, but it is clear that they bear no apparent relation to the original titer of hormone injected, probably representing variations in the reactivity of the individual frog. All tests have been performed on adult male frogs run in pairs, the animals being obtained from local collectors. However, since the animals used are captured in the wild state and since estimation of age, to say nothing of sex, is difficult, it would be wise when possible to use 3 animals per test, simply to lower the mathematical probability of encountering all immature or superannuated animals on any given specimen of urine. Although this difficulty in selecting suitable animals may be of some theoretic significance, practically speaking our results indicate that it has not offered any real problem. For similar reasons it is probably good practice to open all "negative test" frogs simply to ascertain by inspection of the gonads that the animals used are male, the external features being insufficiently characteristic for most workers to separate definitely males from females.

RESULTS

The results are presented and discussed under each of four headings cited above.

Possible Pregnancy

As mentioned earlier this category is meant to include patients who present themselves to the physician as possibly pregnant with a history of a missed menstrual period or some disturbance in the regularity of the menstrual cycle. A total of 242 urine tests fall into this group, with the following results: correct positive, 113, correct negative, 117, false positive, 1, and false negative 11.

With relation to the correct-positive reactions, it is obvious that these tests merely indicate the presence of an apparently uncomplicated early pregnancy. It is well known that at the beginning of pregnancy the titers of gonadotropin are extremely low and only begin to rise to any appreciable level after approximately fifteen days of gestation. Since many urine samples are submitted for analysis after only one or two days of amenorrhea, some even before the first missed period, it did not seem justifiable to call these extremely early negative tests false negative. It was arbitrarily decided, therefore, that fifteen days after the first missed period was

the earliest date at which a negative test would be accepted as incorrect. Therefore any negative tests before this arbitrary time limit were not considered false negative. Admittedly, fifteen days of amenorrhea comprises a somewhat long wait before a diagnosis is attempted. However, performance of a test before this time involves a calculated risk. When such tests are negative, despite the presence of a viable early pregnancy, considerable clinical confusion invariably follows. If the problem involved in doing tests within the first two weeks of amenorrhea is appreciated, only positive results should be considered as having value. In this same regard 13 tests performed on specimens of urines from patients who were within fifteen days of the first missed period were correctly positive. In fact,

suggesting the likelihood of an abnormal conception or implantation. Tests indicated in Table 1 as numbers 7 to 10 were performed on specimens derived from patients in the third and fourth months of pregnancy. Hormone titers at this time while rapidly falling should nonetheless certainly be detectable. Tests No. 7 and 8 are samples of urine from the same patient, a curious case of undoubted abnormality. The case was thought to represent an intrauterine fetal death with missed abortion, since the size of the uterus never conformed to the calculated duration of the amenorrhea. Two male frog tests were negative, and yet five months later, at a calculated nine months of gestation, a small infant of approximately five months fetal size was born alive and died within two days. Under these

TABLE 1 *False-Negative Reactions*

TEST No	PATIENT	AGE	PERIOD OF AMENORRHEA AT TIME OF PERFORMANCE OF TEST	CLINICAL HISTORY
1	M P C	37	22	Normal pregnancy
2	L H C	34	18 days	Patient pregnant at time of test miscarried 1 mo later
3	C K	—	21 days	Normal pregnancy
4	B B	24	16 days	Normal pregnancy
5	B S B	22	21 days	Normal pregnancy urine specimen received by mail after several days of nonrefrigeration
6	L K	—	16 days	Normal pregnancy
7	E P	28	21 days	Normal pregnancy Patient said to be 9 months pregnant, delivered 5 mo size infant which lived 2 days
8	E P	28	4 mo	Repeat test on above patient
9	M J	26	3 mo	Normal pregnancy urine specimen received by mail
10	M D	—	4 mo	Normal pregnancy
11	T F	—	5 wk	Normal pregnancy

4 specimens were within the first four days after the first missed period. These results are of interest only so far as they indicate that the male frog will react to some early pregnancies, even as the immature rat and rabbit. The 117 correct-negative reactions comprise a mixed group of patients: 10½ with simple amenorrhea, 4 with beginning menopause, and 9 with very early pregnancies that fell within the interval of the first two weeks of amenorrhea mentioned above.

False-negative results merit careful attention and are considered in Table 1.

It can be seen that the first 6 false-negative tests cited were performed on patients within the period of fifteen to twenty-one days of the first missed period. It is entirely possible that these urine samples represent pregnancies with poor production of gonadotropin, since it is well known that individual pregnancies vary greatly in the quantity of hormone excreted. Extreme instances have been cited in which no detectable gonadotropin could be demonstrated throughout a normal pregnancy. In support of the possibility that some of these false-negative tests were due to low-titer urines is the fact that in Case 2 the patient spontaneously miscarried at two and a half months of gestation,

peculiar circumstances, whether the negative frog tests are justifiably considered as falsely negative is a controversial point. Other factors, such as deterioration of the hormone titer of the urine while the specimen is in transit by mail, contributed to the above so-called false-negative results.

The solitary false-positive result encountered in the entire series of 300 tests fell into this group of so-called early normal pregnancies. The patient was a thirty-eight-year-old woman entering the hospital with intense jaundice, apparently of the obstructive type, and associated amenorrhea of two months' duration. The urine specimen submitted for hormonal assay was intensely icteric, giving a positive result on male frogs. Subsequently the patient died, and autopsy demonstrated an obstructing stone in the common duct, bile stasis of the liver with early biliary cirrhosis and a terminal acute hemorrhagic pancreatic necrosis. No evidence of pregnancy could be found. Many speculations might be offered to explain this positive result. Suffice it to say that bile added to normal urine has no effect on the male frogs. Estrogens do not produce spermatism in these animals, and at the present time no good explanation exists for the effect of this type of urine on male frogs. For the

time being therefore, we have avoided icteric urines and thus have not re-encountered this problem

Possible Ectopic Pregnancy

This small group of urines (5 specimens) was derived from women all proved to have ectopic pregnancy by surgical exploration. In most, the presenting clinical features were those of lower abdominal pain and some pelvic mass associated with a disturbance of the regular menses. In the child-bearing age ectopic pregnancy was considered as the probable diagnosis and a urine sample was subsequently submitted for hormonal assay. In 3 cases correct-positive results were obtained, the periods of amenorrhea in the 2 known cases being one month and three months. In another case the urine was submitted before the patient had missed her first period, and the result was negative, as was fully anticipated. Such a result cannot justifiably be termed a false negative. In the last case the patient was three weeks overdue, the frog test was negative, and at laparotomy a tubal pregnancy was found. In the aggregate these results compare favorably with those obtained with the use of any other type of laboratory animal.

Possible Fetal Death

This group of tests is one of the most difficult to evaluate. Patients most of whom are known to be pregnant, begin to have vaginal bleeding, and the question of the viability of the fetus arises. Urine assay remains the only technic presently available for determining viability. Since the exact time of fetal death is seldom, if ever, clear clinically, it is most difficult to ascertain with any surety the exact status of the pregnancy at the time of obtaining the urine sample for assay. Thus, of the many cases of this type tested at this laboratory most had to be discarded. Only cases in which the status of the fetus could be determined fairly certainly at the exact time of performance of the urine test were included in this series. Thus, the total number of acceptable specimens was 23. No incorrect results were encountered. There were 6 correct-positive tests in which it was possible to show that fetal death had not occurred prior to the test and 17 correct-negative tests in which unequivocal evidence, such as passage of placental tissue, indicated the certain death of the fetus. Admittedly, this category has little critical value in the evaluation of a test for pregnancy. The difficulty in judging the clinical course of the pregnancy is so great that when the pregnancy test and the clinical status fail to agree it may well be the clinical impression that is in error. Thus, so-called false results in this group have little real significance since they may simply represent misinterpretation of the clinical status at any given time.

Pelvic Mass

The last group of tests as the heading indicates, is derived from patients having a large pelvic mass representing either a tumor or a pregnancy or both. Seventeen tests comprise the total, and all were received from patients with either uterine leiomyomas or ovarian cysts. No cases of concomitant pregnancy were encountered, and all the tests were correctly negative.

The remainder of the series of 300 tests here reported were made up of tests performed on patients being studied postoperatively after surgical removal of a hydatidiform mole. All these thirteen tests were negative and agreed with the clinical follow-up study of the patients, some for as long as two years.

DISCUSSION

The results already cited for the various categories are summarized in Table 2. It can be seen that of the series of 300 urine tests performed incorrect results were encountered in 13. Thus, the over-all accuracy of this technic may be cited as approximately 96 per cent. One of the incorrect results was falsely positive, the remaining 12 being

TABLE 2 *Results of Pregnancy Test*

ACTUAL DIAGNOSIS	CORRECT-POSITIVE TESTS	CORRECT-NEGATIVE TESTS	FALSE-NEGATIVE TESTS	FALSE-POSITIVE TESTS
Possible pregnancy	113	117	11	1
Possible ectopic pregnancy	3	1	1	—
Possible fetal death	6	17	—	—
Pelvic mass	—	17	—	—
Hydatid moles (follow up study)	—	13	—	—
Totals	122	165	12	1

falsely negative. In terms of false-positive results, the most important consideration, the error was a third of 1 per cent. In addition, it is well to remember that this single false-positive test was encountered in the urine of a patient with intense obstructive jaundice, and although the ultimate basis for this false-positive reaction is still obscure, repetition of the incorrect result can be avoided simply by the rejection of all such icteric urine specimens. Of interest is the fact that an additional sample similar to the one described above was received recently, and although no diagnostic report was submitted, the urine gave a positive test on the male frogs. It was later determined that the patient was not pregnant, implying that the substance present in this icteric urine behaved like the substance present in the earlier, similar specimen. Further study of this problem is now in progress.

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This analysis indicates that the male frog test is a procedure of sufficient specificity and sensitivity to merit further use and investigation. Although the frog fails to achieve the accuracy of

the immature rat in the Aschheim-Zondek test, the many other advantages of the use of the frog seem to outweigh this small difference in sensitivity. In competent hands the Aschheim-Zondek test employing immature rats achieves an accuracy of close to 99 per cent, compared with the 96 per cent of the frog test. This difference in sensitivity is of some theoretic interest since repeated parallel assays of urine samples on rats and frogs indicate a complete identity of sensitivity to gonadotropins for the two types of animals. The theoretic basis, therefore, for this difference in accuracy between the rat and frog is totally obscure.

The results here reported are intended to serve as a progress report and possible stimulus to further modification and investigation of this technic. In this regard, we are privileged to include several suggestions, as yet unreported, that may well enhance the accuracy of this test to a point where it will compare favorably with all other technics.

Goodof,⁸ having available an abundant source of vigorous frogs, submits all newly received animals to a screening injection of a minimal reacting dose of chorionic gonadotropic hormone. Frogs failing to respond to this dosage level are discarded. By this means females, poorly developed males and subreactive animals are eliminated, and only known reactors are then used for diagnostic work. More recently, Elrich, Albright and Brenner,⁹ working with the male *Rana pipiens*, encountered a high percentage of toxic urines. To avoid this problem, dialysis of whole urine against slowly running cold tap water for an hour was employed, following similar technics by Heller et al.¹⁰ After this treatment it was found that all urine specimens were completely nontoxic, and therefore 10 cc of urine was employed as the routine injection dose, doubling the size of the previous dose. Heller and Chandler¹⁰ have shown that no hormone titer is lost in this dialysis treatment, and, therefore, with the use of 10 cc of urine the sensitivity of the frog test has been appreciably increased. To date no false results have been encountered by these workers. The increased dosage that dialysis permits may well bring the accuracy of the frog test up to the level of the Aschheim-Zondek procedure. Another method of handling toxic urines has been used recently.¹¹ It comprises the precipitation of the hormone by the use of a mixture of ether and 95 per cent alcohol. The precipitate obtained is dissolved in saline solution and injected. This method is said to permit the use of larger volumes of urine and thus to enhance the sensitivity of the test. Moreover,

the simple use of 3 frogs for each urine assay may well enhance the accuracy of this technic by mathematically lowering the probability of encountering all nonreactive animals. What effect on the accuracy of the male-frog test these various modifications may have is as yet not known, however, they bear promise for the future.

SUMMARY

Three hundred routine, essentially consecutive urine specimens have been submitted to pregnancy hormonal assay utilizing the male-frog (*Rana pipiens*) test.

An over-all accuracy of approximately 96 per cent has been achieved. A single false-positive test, now believed to be readily avoidable, and 12 false-negative reactions were encountered.

The analysis of the results indicates that most of the false-negative reactions were encountered in cases of normal pregnancy within the first month of amenorrhea. Yet several positive tests were obtained in other cases within the first four days of amenorrhea, indicating that the problem is not one alone of insensitivity of the frog to chorionic gonadotropin, but of varying hormone levels in individual pregnancies.

The results obtained appear to justify the continued use and study of this diagnostic technic. Several possible modifications having considerable promise are mentioned.

Since this paper was submitted for publication the technic for the performance of the test has been modified. Twenty cubic centimeters of urine per frog is precipitated with 4 vol of 95 per cent alcohol. The sediment obtained by vacuum filtration is dissolved in saline solution and injected. The results appear to be somewhat superior to those obtained with whole urine.

We are indebted to Mrs. Phyllis B. Marshall and Miss Gloria E. Mannix for their technical assistance.

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FATAL PANCYTOPEMIA FOLLOWING THE USE OF "MESANTOIN"*

Report of a Case

RUSSELL W. WELLER, M.D.,† AND JAMES METCALFE, M.D.‡

NEWPORT, RHODE ISLAND

"MESANTOIN" (3-methyl-5, 5-ethylphenyl-hydantoin), a close chemical relative of dilantin has been used as an anticonvulsant in the treatment of grand-mal seizures since 1945. In 1946 Harrison, Johnson and Ayer¹ reported a case of fatal aplastic anemia following the use of "mesantoin" and tridione. Since that time several cases of pancytopenia following the use of "mesantoin" have been reported.^{2, 3} The following case of fatal pancytopenia occurring after the use of "mesantoin" is presented to stimulate further investigation of the properties of this drug.

CASE REPORT

L. V. D., a 31-year-old veteran of World War II entered the United States Naval Hospital, Newport, Rhode Island, on January 7, 1949, complaining of bleeding from the right nostril of 2 days' duration. The nostril had been packed by his physician, but bleeding continued. He was admitted to the ear, nose and throat service, where local treatment with silver nitrate, fibrin foam and two blood transfusions of 500 cc each failed to stop the bleeding. On January 12 he was transferred to the medical service, where it was learned that he had been taking "mesantoin" and phenobarbital for 6 months prior to entry because of "epileptic attacks," which allegedly followed a skull fracture in 1944. He had continued to take "mesantoin" in a dosage of 0.1 gm daily until January 6, and had taken none since.

There was no family history of bleeding abnormality, and he had no past history of joint pains, visceral pain or hemorrhagic tendencies. He had noted no hematuria, hematemesis or melena.

Physical examination on January 12 revealed a pale thin man in no acute distress. The right nostril contained a large, dark clot from beneath which oozed bright-red blood. There was a linear depression of the skull in the left frontal area. There were numerous discrete petechial hemorrhages in the skin over the entire body varying from pin-point size to 5 mm in diameter. The mucous membranes were pale, and the uvula was swollen and dark. There was no palpable lymphadenopathy, the lungs were clear, and the heart was normal to physical examination except for the tachycardia. The liver edge was just palpable beneath the right costal margin and the spleen could not be felt. Neurologic examination revealed no abnormalities.

The temperature was 101.2°F by mouth, the pulse 120, and the respirations 20. The blood pressure was 125/80.

Examination of the blood disclosed a red-cell count of 3,350,000, with a hemoglobin of 9.8 gm per 100 cc. The urine was normal, and smears for malaria were negative. The bleeding time was 2 minutes, the coagulation time 2½ minutes (Lee and White method), and the clot retraction was very poor. On the 5th hospital day the red-cell count was 2,130,000, with 6.23 gm of hemoglobin, and the white-cell count 1850, with 86 per cent lymphocytes and 14 per cent neutrophils. The color index was 0.98, and a smear of the peripheral blood revealed anisocytosis, poikilocytosis and toxic granulation of the neutrophils. The prothrombin time (Quick quantitative method) was 15 seconds (control, 13 seconds), and the blood urea nitrogen 17.8 mg per 100 cc of whole blood. Sternal-marrow aspiration smears revealed an aplastic marrow with an average of 1 normoblast in six oil immersion fields. The icteric index was 10, the cephalin-flocculation reaction + + + +, and the platelet count 36,000.

*The opinions and assertions contained herein are the ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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In spite of the measures outlined below the pancytopenia progressed, with a red-cell count of 1,880,000 and a white-cell count of 1400 on the 9th hospital day. On the 14th day (the day of death) the red-cell count was 1,910,000, the white-cell count 1000, and the platelet count 24,000.

The patient was treated with daily transfusions of whole blood, intramuscular injections of penicillin, liver extract and "pentnucleotide," intravenous administration of vitamin K, oral administration of vitamin C, folic acid and yellow bone marrow. After each blood transfusion his temperature rose, but there were no other manifestations of a transfusion reaction. A tourniquet test on January 13 yielded complete ecchymosis in the test area. This test was repeated on January 19, when only 10 pin-point petechiae were obtained in the test area. This change in response coincided with the clinical impression of improvement, although the laboratory findings gave an entirely different view, and his temperature remained elevated, spiking to 105°F after each transfusion. On January 20 a chest x-ray film showed mottled pneumonic infiltration in the left mid-lung field. X-ray films of the long bones were normal. Penicillin was continued.

On the morning of January 22 the patient was found unconscious in bed. Respirations were labored, and the cardiac rate was 96, with distant heart sounds. Moist rales were audible scattered throughout both lung fields. He was placed in an oxygen tent, but respirations ceased shortly thereafter.

Post-mortem examination revealed petechial hemorrhages in the skin of the extremities, chest and abdomen. There was a large amount of dried blood in the nares and pharynx. Diffuse subpericardial and subpleural hemorrhages were present, as well as subserosal hemorrhages of the entire gastrointestinal tract. There were subcapsular hemorrhages of both kidneys, as well as submucosal hemorrhages of the pelvis and ureters. Numerous large, poorly defined hemorrhagic areas were seen in both lungs, along with a moderate amount of pulmonary edema and carnification of the left lower lobe with pleural thickening. Examination of the brain showed several large subdural hemorrhages and large areas of cortical necrosis on the ventral aspects of the frontal and temporal lobes extending into the white matter. Many recent hemorrhages were present in the frontal, parietal and temporal cortex. The bone marrow was yellowish brown.

Microscopic examination disclosed terminal subendocardial and subepicardial hemorrhages, with early necrosis of the adjacent myocardium. There was moderate pulmonary edema, organizing lobar pneumonia in sections from the left lower lobe and recent hemorrhage into the alveoli in many sections. Recent and older partially absorbed hemorrhages were present in the cerebral cortex and white matter, and advanced cortical necrosis was observed. The sternal-marrow blocks showed marked aplasia with increased fat, reticulum cells, a rare erythroblast and a rare myelocyte. No megakaryocytes were seen.

SUMMARY AND CONCLUSION

A case of fatal pancytopenia following the use of "mesantoin" and phenobarbital is presented. Autopsy revealed multiple visceral and cutaneous hemorrhages, an organizing lobar pneumonia and an aplastic bone marrow.

Accumulating evidence suggests that further investigation of the possible toxic properties of "mesantoin" is advisable.

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the immature rat in the Aschheim-Zondek test, the many other advantages of the use of the frog seem to outweigh this small difference in sensitivity. In competent hands the Aschheim-Zondek test employing immature rats achieves an accuracy of close to 99 per cent, compared with the 96 per cent of the frog test. This difference in sensitivity is of some theoretic interest since repeated parallel assays of urine samples on rats and frogs indicate a complete identity of sensitivity to gonadotropins for the two types of animals. The theoretic basis, therefore, for this difference in accuracy between the rat and frog is totally obscure.

The results here reported are intended to serve as a progress report and possible stimulus to further modification and investigation of this technic. In this regard, we are privileged to include several suggestions, as yet unreported, that may well enhance the accuracy of this test to a point where it will compare favorably with all other technics.

Goodof,⁸ having available an abundant source of vigorous frogs, submits all newly received animals to a screening injection of a minimal reacting dose of chorionic gonadotropic hormone. Frogs failing to respond to this dosage level are discarded. By this means females, poorly developed males and subreactive animals are eliminated, and only known reactors are then used for diagnostic work. More recently, Elrich, Albright and Brenner,⁹ working with the male *Rana pipiens*, encountered a high percentage of toxic urines. To avoid this problem, dialysis of whole urine against slowly running cold tap water for an hour was employed, following similar technics by Heller et al.¹⁰ After this treatment it was found that all urine specimens were completely nontoxic, and therefore 10 cc of urine was employed as the routine injection dose, doubling the size of the previous dose. Heller and Chandler¹⁰ have shown that no hormone titer is lost in this dialysis treatment, and, therefore, with the use of 10 cc of urine the sensitivity of the frog test has been appreciably increased. To date no false results have been encountered by these workers. The increased dosage that dialysis permits may well bring the accuracy of the frog test up to the level of the Aschheim-Zondek procedure. Another method of handling toxic urines has been used recently.¹¹ It comprises the precipitation of the hormone by the use of a mixture of ether and 95 per cent alcohol. The precipitate obtained is dissolved in saline solution and injected. This method is said to permit the use of larger volumes of urine and thus to enhance the sensitivity of the test. Moreover,

the simple use of 3 frogs for each urine assay may well enhance the accuracy of this technic by mathematically lowering the probability of encountering all nonreactive animals. What effect on the accuracy of the male-frog test these various modifications may have is as yet not known, however, they bear promise for the future.

SUMMARY

Three hundred routine, essentially consecutive urine specimens have been submitted to pregnancy hormonal assay utilizing the male-frog (*Rana pipiens*) test.

An over-all accuracy of approximately 96 per cent has been achieved. A single false-positive test, now believed to be readily avoidable, and 12 false-negative reactions were encountered.

The analysis of the results indicates that most of the false-negative reactions were encountered in cases of normal pregnancy within the first month of amenorrhea. Yet several positive tests were obtained in other cases within the first four days of amenorrhea, indicating that the problem is not one alone of insensitivity of the frog to chorionic gonadotropin, but of varying hormone levels in individual pregnancies.

The results obtained appear to justify the continued use and study of this diagnostic technic. Several possible modifications having considerable promise are mentioned.

Since this paper was submitted for publication the technic for the performance of the test has been modified. Twenty cubic centimeters of urine per frog is precipitated with 4 vol of 95 per cent alcohol. The sediment obtained by vacuum filtration is dissolved in saline solution and injected. The results appear to be somewhat superior to those obtained with whole urine.

We are indebted to Mrs. Phyllis B. Marshall and Miss Gloria E. Mannix for their technical assistance.

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of the United States) any increase in diphtheria will be likely to affect adults relatively more than children. For effective immunization in children should leave only a small proportion unprotected—perhaps 2 to 10 per cent—whereas the figures of Schick²⁵ and others indicate that at least 15 to 20 per cent of adults are Schick positive and therefore presumably susceptible to diphtheria. Moreover the early observations of Park²⁶ variously confirmed during the last twenty years have shown that these figures are representative only for adults from urban or otherwise congested areas far higher Schick-positive rates being found among many adult groups. Twenty-five years ago White²⁷ in Massachusetts, found 75.5 per cent of country school-teacher's, 77 per cent of Smith College students and 35 per cent of all adults surveyed to be Schick positive.²⁷ A similar observation²⁸ made by Crooks in 1925²⁸ is true, that some recent surveys have found no more than 24 to 30 per cent Schick-positive reactors among American military personnel²⁹⁻³² and even lower rates have been noted elsewhere³³⁻³⁵. But numerous other reports disclose much higher Schick-positive rates among Americans—for example 29 to 45 per cent in medical students³⁶ 49 per cent and 70 per cent in student nurses³⁷ 35 40 per cent in prison inmates and 51 per cent to 82 per cent in parents or teachers³⁹⁻⁴⁰ 34 per cent in 18,000 Navy recruits⁴¹ and 42 per cent in a smaller Navy group⁴² and 44 per cent in 2983 Army personnel⁴³. In other countries similar figures have appeared from 42 to 87 per cent positive reactors among various adult groups in Canada⁴⁴, 46 to 60 per cent among Australian medical and nursing students⁴⁵, 51 per cent among English mothers⁴⁶, and 67 per cent among Norwegian mothers⁵⁰. Finally diphtheria may occur under some conditions in persons who have immunity equivalent to the level of a negative Schick test, Ipsen⁵¹ has reported a series of cases observed during the wartime epidemic in Denmark, in which diphtheria occurred despite an immunity level far above the accepted minimum supposedly adequate for protection. Thus, it is necessary not only to revise established concepts regarding the general level of Schick positiveness in adults but also to re-emphasize the fact that a negative Schick test is not an infallible indication of immunity.

Efficacy of Immunization

One may ask at this point, What evidence is there that diphtheria immunization is actually effective? What have been the actual proved results following its use? Certain of the answers to this question, already summarized,¹¹ indicated that adequate immunization against diphtheria has given as much as 85 to 95 per cent protection. Several recent reports from widely scattered areas have supported these figures⁵²⁻⁵⁵. However a few studies have not been so optimistic, showing only

about a 50 per cent protection rate⁵⁶⁻⁵⁹. Practically all reports note that cases in the immunized, where they do occur are relatively mild with few or no deaths. In a Swedish series for example, the death rate was 1.6 per cent (1 in 61) in inoculated compared to 11.7 per cent (24 in 267) among the uninoculated patients⁵⁵. This is strikingly confirmed by Ipsen,⁵¹ who observed 8.7 per cent deaths among 287 unvaccinated patients as against no deaths among 138 partially or completely vaccinated patients. Poulain²¹ likewise reported 30 deaths in 490 unvaccinated and no deaths in 90 vaccinated patients.

It has been noted previously¹¹ that some failures to achieve protection can be ascribed to a lack of understanding of how to use diphtheria toxoid—for example, the use of two doses of fluid toxoid or one dose of alum toxoid or the administration of any kind of toxoid at one-week intervals. In other instances failure may correctly be attributed to the use of toxoids of insufficient potency. Such instances have been detected by careful observers in England⁶⁰ and Denmark.⁶¹ One wonders whether such a factor played a part in the severe outbreak reported by Fanning⁶² in an English girls' school. Fifteen cases of diphtheria occurred among 299 previously immunized students, whereas 3 occurred among 23 unimmunized pupils. Although 96 per cent of the pupils had been immunized, only 69 per cent were Schick negative. However, several of the cases were in children who had just previously shown a negative Schick test.

In any attempt to evaluate the efficiency of diphtheria immunization, the rate at which immunity wanes must also be considered. It was previously noted¹¹ that anywhere from 3 to 20 per cent reversion to the Schick-positive state has been seen at the end of a year, these studies and others indicate that over a period of four or five years anywhere from 12 to 35 per cent relapses from immunity to susceptibility may be expected⁶³⁻⁶⁵.

In summary, then it appears that from as little as 50 per cent to over 90 per cent protection may be expected from adequate diphtheria immunization, and that in any case the complication and mortality rate in immunized persons will be very low. However, it is unfortunate that few, if any, truly controlled studies on the results of diphtheria immunization have been carried out, so that the efficacy of this procedure cannot be assessed as precisely as for example, that of influenza and pertussis immunization. To be sure, the incidence and severity of diphtheria in many immunized groups have been compared with rates in unimmunized subjects. However, there is little evidence in most such reports that the controls were of comparable economic status, hygienic habits, family size and so forth. Consequently, the claims for diphtheria immunization have been vulnerable to the attacks of the skeptics, among the most ingenious, persistent and

MEDICAL PROGRESS

ACTIVE IMMUNIZATION

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DURING the past three years there have been many general and special contributions to the subject of active immunization. The principles and practices of pediatric immunization have been discussed in some detail by Miller,¹ who has long combined both practice and research in this field. The latest revision of the American Academy of Pediatrics *Handbook*² takes note of most of the recent revisions in immunization practices and provides, as always, many thought-provoking statements and opinions. Along a different train of thought, Parish³ has presented a stimulating discussion of the present knowledge regarding both principles and practices of prophylactic inoculation, together with a consideration of probable future trends. Top,⁴ as one of several participants in a symposium on immunization procedures,^{4,5} has denoted the criteria that are helpful in assessing the value of an immunizing agent: safety, effectiveness, usefulness and ease of administration. His brief paper illustrates these principles, and considers their significance for both the health officer and the physician in private practice. A further item of usefulness for the practitioner is a pamphlet⁶ recently issued by the United States Public Health Service, summarizing recommended immunization procedures prior to foreign travel.

Most of the problems underlying the principles of immunization remain little advanced as compared to the situation two or three years ago, in some fields, however, new information of significance has appeared. Freund,¹⁰ in a scholarly review of certain aspects of this field, gives particular consideration to the cells responsible for antibody formation, and to the use of adjuvants for enhancement of the immunizing effect of an antigen. Several other lines of research are now being actively pursued by numerous investigators, and may lead within the next few years to significant advances in the understanding of the basic mechanisms that underlie immune phenomena. Meanwhile, it is of value to consider the advances of a somewhat more empirical nature that have taken place in the control by immunization of certain diseases of importance in the northeastern United States: diphtheria, influenza, pertussis, pneumonia, rabies, smallpox, tetanus, tuberculosis and typhoid fever. A previous review¹¹ considered all these diseases except pneumonia and tuberculosis, and also included scarlet fever. Little new information has appeared

regarding immunization against the latter disease, except for a few studies using precipitated antigens,^{12,13} which show promise but require more extensive trial. The present review has of necessity included further consideration of many problems taken up in the 1946 review, space forbids the recapitulation of many developments that were previously considered, and reference is made to the earlier publication for such material when it relates to current findings.

DIPHTHERIA

Recent Trends

Increase in adults. The wave of diphtheria that swept over most of Europe during the recent war has been well summarized by Stowman.¹⁴ The possible effects of this epidemic on diphtheria trends in the United States have been considered in detail by several writers.^{15,17} Whether many new and virulent strains were introduced into this country from Europe, or whether the increase of cases in recent years in the United States was due primarily to domestic factors, as Anderson believes,¹⁶ there is no doubt that marked increases in both the incidence and the severity of diphtheria have been noted in various sections of this country. The rise began to be noticed about 1940, passing its maximum at different times in different localities. Nowhere in the United States were these increases at all comparable with the twentyfold increases observed during the height of the Norwegian and Dutch epidemics. Nevertheless, the fact that a threefold or fourfold increase should occur in a community such as Massachusetts, where extensive immunization programs have been carried out for many years, has called for a re-examination of the factors that determine susceptibility or resistance to diphtheria in the individual as well as in the herd.

One of the outstanding trends in the recent pandemic of diphtheria has been the marked increase in the percentage — and indeed often in the actual numbers — of adult cases. This has been noted in Massachusetts and has been reported from many widely separated areas — such as Minnesota,¹⁸ California,¹⁹ Utah,²⁰ France,²¹ Italy,²² Denmark²³ and Germany²⁴ — and in fact has been characteristic of the entire diphtheria picture in Europe.¹⁴ This shift appears to have been due to two factors. The first is the obvious fact that, where immunization among children has been extensively carried out (as in Denmark, parts of France and many areas

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achieve much purification, or to the unusually large amount of toxoid protein that they injected Holt,⁸² ⁸³ of the Wright-Fleming Institute in London, has described a method of preparing a purified aluminum-phosphate-adsorbed toxoid of constant composition, which is relatively free from impurities and highly antigenic Bousfield⁸⁴ ⁸⁵ has reported very satisfactory results from its clinical use Using a different approach Ross⁸⁶ has eliminated a large proportion of the nonbacillary toxoid protein by precipitation with protamine Pillemer,⁸⁷ applying alcohol fractionation in the cold, has obtained a toxoid that is over 90 per cent pure Levine et al⁸⁸ have prepared toxoid of similar purity by ammonium sulfate fractionation All these preparations have proved to be antigenic, and well tolerated in children,⁸⁴ ⁸⁶ ⁸⁹ but such meager data as are available regarding their reactivity in adults indicate that reactions have not been entirely eliminated The recent findings of Pappenheimer and Lawrence⁹⁰⁻⁹² may explain much of the difficulty that has been experienced in this respect Using very highly purified reagents, they demonstrated, in careful quantitative animal studies, that toxoid protein and the other bacillary protein or proteins present in crude toxoid are both antigenic, but are immunologically distinct⁹⁰ They showed that human subjects may be separately sensitive to either toxoid or bacterial protein, or to both, and that this sensitivity may be elicited by extremely small quantities of either substance⁹¹ In general, their subjects who had low antitoxin titers were relatively insensitive to the toxoid protein, whereas exquisite sensitivity to this fraction was rather common among immune subjects Sensitivity to bacterial protein was not closely correlated with serum antitoxin levels, although it was in general more marked in immune subjects Finally, Pappenheimer and Lawrence⁹² have demonstrated that immunity can be produced without discomfort by employing normal doses of purified toxoid in hyposensitive subjects, and reduced doses in hypersensitive subjects This clearcut demonstration that acute sensitivity can exist to toxoid protein may require extensive revision of present concepts of diphtheria immunization, particularly in adults Whatever the final answer may be, it is probable that the use of purified toxoid will become essential, and it is also likely that some sort of control or sensitivity test will still be required in adults before even a purified toxoid can be administered with impunity

Neonatal Immunization

It has long been recognized that the passive transfer of maternal immunity to the newborn infant interfered with neonatal immunization up to the time that such immunity is lost, toward the end of the first half year of life Cooke⁹³ has recently confirmed this by administration of combined diph-

theria-tetanus toxoid to 284 infants, demonstrating a good response to diphtheria toxoid in infants lacking maternally transferred antibodies to diphtheria, a relatively poor response in young infants inheriting passive immunity, and a uniformly good response to tetanus toxoid regardless of age, since there is no inherited immunity against tetanus toxoid These results indicate that too much dependence should not be placed on neonatal immunization of infants against diphtheria However, the use of an antigen potentiated by admixture with adjuvants or combined with other antigens, such as pertussis bacilli, may overcome the handicap inherent in neonatal antidiphtheric immunization Bell⁷⁴ found that 201 infants under six months, who received alum-precipitated toxoid combined with pertussis vaccine, showed essentially the same Schick-negative rate a year later, as was found in 236 older infants given alum-precipitated toxoid alone, and di Sant' Agnese⁹⁴ has observed that the booster response in both age groups is equally good one year after primary immunization

INFLUENZA

Effectiveness of Immunization

Several comprehensive reviews on influenza⁹⁵ and in particular on vaccination against influenza⁹⁶ ⁹⁷ have recently summarized the principal developments of the past few years in the control of this disease As noted in previous reviews,¹¹ ⁹⁵ the large-scale vaccination studies of 1943-1944 in Army personnel showed an influenza attack rate of 2.22 per cent in the vaccinated as against 7.11 per cent in the controls A similar outbreak in an institution,⁹⁸ analyzed in a subsequent report,⁹⁹ showed attack rates of 1.9 per cent in the immunized and 12.4 per cent in the unimmunized — roughly a 6.1 protection rate The next major outbreak, a Type B epidemic in 1945-1946, was studied on two college campuses in this country, where vaccinated Army personnel and unvaccinated Navy personnel were concurrently exposed The protection rates observed in the two studies were 9.1¹⁰⁰ and 24.1¹⁰¹ Simultaneously, a Type B outbreak in England gave opportunity for observing the effects of vaccine in that country, protection rates ranging from 2.1 to 5.1 in different groups were observed¹⁰² On the basis of such observations as these, there appeared to be many valid indications for use of influenza vaccine, even though the apparently short duration of the immunity obtained and the slight but definite danger of reactions were fully recognized¹⁰³ Vaccination was recommended for use in persons with histories of severe influenza, in groups where absenteeism would create significant problems, in crowded colleges and technical schools, and so forth¹⁰³ Some clinicians emphasized the value of immunization for "the very large group of infants and children from several months of age

iconoclastic of whom is Rendu⁶⁶ in Lyon, France. According to Rendu, for example, although the immunization of school children in Geneva in the 1930's was followed by a decrease in diphtheria, there was also a comparable decrease in uninoculated areas, and the recrudescence of diphtheria in Geneva in 1941-1944 was as marked as it was in Neuchâtel, where no immunization program had been carried out. In another article, Rendu⁶⁷ undertakes to refute a series of French reports on the striking effect of toxoid in aborting diphtheria outbreaks in civilian and military personnel. In a recent paper he⁶⁸ dissects some of the data regarding diphtheria immunization in the French Army, particularly with reference to an extensive program for immunizing Schick-positive soldiers, which was claimed by Dopter⁶⁹ to have led to an eightfold reduction in the incidence of the disease among those immunized. These results were based on the premise that all soldiers developing diphtheria prior to completion of immunization should be classed as "unimmunized", as would be expected, a large proportion of cases occurred in this group, since they were invariably new recruits. Rendu challenges this premise and shows that, if all such cases are classed as "immunized," there is no difference in the diphtheria incidence between "immunized" and "unimmunized" troops. Obviously, one cannot accept either Dopter's assumption (that Schick-positive, inoculated troops can be compared with Schick-negative, uninoculated troops) or the extraordinary concept of Rendu that, if a man is scheduled to be injected, he shall be classed as "immunized." Such fallacies weaken Rendu's strongest argument, which is that many items of "evidence" for the efficacy of toxoid are actually inconclusive. Nevertheless, his widespread statements that diphtheria toxoid is not only useless but also perhaps harmful have led in some quarters to a reluctance in accepting immunization. Poulain,²¹ also of Lyon, analyzed the actual results of immunization in that city, and showed that, in each age group, the diphtheria rate in the immunized was about one tenth that in the uninoculated, and furthermore, that no deaths occurred in the immunized persons during the four years of an active immunization program. Furthermore, he presents evidence that, in the last fifteen months of this program alone, 22 deaths in unimmunized children might have been prevented, if about 15 per cent of the population had not ignored or evaded the city's immunization program, in part because of misinformation as indicated above.

Methods of Increasing the Effectiveness of Immunization

Three important approaches may be considered: addition of an adjuvant, increasing the dose, and giving more frequent or more numerous doses. It is well established, for example, that the addition of numerous substances (of which alum is merely

the best known example) will increase the effectiveness of a given quantity of toxoid. Recent laboratory and clinical observations⁷⁰⁻⁷⁴ give strong evidence that a similar effect is achieved by a mixture of toxoid with bacterial suspensions such as pertussis vaccine. Such measures may be of great value in establishing an adequate primary immunity. There is a growing recognition, however, as noted above, that primary immunity will wane sooner or later, and hence that it is necessary to administer "repeat" or "booster" doses at suitable intervals — as when a child first enters school. Numerous studies confirming the efficacy of such a procedure have previously been assembled,¹¹ but the optimum dose for this purpose has yet to be determined. Wishart et al.⁷⁵ gave various quantities of toxin or toxoid to eleven groups totaling 378 persons. They found that 4 flocculating (Lf) units (about 0.1 cc of the usual toxoid) produced an antibody response in over 95 per cent of previously immunized subjects.

Reactions. However, even a 2-Lf dose caused local or general reactions in at least 15 per cent of adults.⁷⁶ In the United States Army, a comparable program elicited marked reactions in 9 to 10 per cent of the subjects injected.⁴³ In another United States Army group the incidence of reaction was apparently reduced by immunization of only the Schick-positive reactors, with graded doses of toxoid.³ However, this is not always practical, and the incidence of reactions found in this study was much lower than that observed in other series. Boyd⁷⁶ attempted to screen a group of 131 British soldiers by testing with Schick toxin and diluted toxoid. The 98 subjects who were not sensitive to the diluted toxoid received 0.2 cc of undiluted alum-precipitated toxoid, almost 40 per cent had severe local or general reactions. A similar experience is reported by Vollum and Wilson⁷⁷ in immunization of nurses. Thus, until a more suitable method for immunization of adults is developed, mass immunization of such groups will continue to present a problem. Another approach to elimination of reactions is to adopt a different route of administration. Masucci, Gold and de Falco⁷⁸ have tried Bousfield's⁷⁹ device, administering toxoid in the form of lozenges placed under the tongue. They observed no untoward reactions, and a good antibody response in previously immunized subjects, but no response in persons who had not previously received immunization, thus they confirmed Bousfield's original observations.

Most recent studies, however, have been directed toward the elimination of the reaction-producing substances in toxoid, which have generally been thought to be the bacterial proteins present in the crude preparation. Peshkin and Rapaport⁸⁰ employed a partially purified toxoid prepared by a calcium phosphate adsorption and elution method.⁸¹ It is difficult to judge whether the severe reactions induced by their product were due to a failure to

Various adjuvants have been employed in efforts to potentiate the effect of a given quantity of influenza virus vaccine. The use of protamine has been suggested¹³⁵ and tried with but indifferent success.¹³² Alum adsorption did not produce a gain.¹³⁹⁻¹⁴⁰ Results of procedures employing calcium phosphate as an adsorbent¹⁴¹ have been inconsistent¹³⁵ but on the whole promising.¹⁴² The most striking effects have been observed after the use of water-in-oil emulsions after the method of Freund.¹⁴³ Influenza virus emulsions of this type have proved to be highly antigenic both in animals¹⁴⁴ and in man.¹³² The relatively high incidence of abscess formation induced by this method, however, is a drawback that has not at present been overcome.

Other Immunization Routes

Intracutaneous vaccination with one or two doses of 0.1 cc of influenza vaccine has been tried, with results superior to those obtained with the standard subcutaneous route employed simultaneously in a control group.¹⁴⁵ Moreover, local and systemic reactions following the intracutaneous vaccine were markedly fewer than those with subcutaneous vaccination. Weller, Cheever and Enders¹⁴⁶ have likewise obtained adequate antibody responses after intracutaneous vaccination. In view of the fact that influenza vaccination is probably in most instances actually a booster procedure,¹⁴⁷ and that intracutaneous immunization is in general highly effective as a booster agent in many conditions, there appears to be a strong case for use of this route as a general procedure.

Since the earliest studies on the virus of influenza, efforts have been made to immunize human beings by inhalation of active or inactive virus. The logic of such an approach is fortified by the finding that influenza virus combines directly with cells of the respiratory tract in a specific manner analogous to the well known reaction of the virus with erythrocytes.¹⁴⁸ The broad pathogenic significance of this reaction has recently been illuminatingly reviewed by Burnet.¹⁴⁹ A series of experimental studies by Australian workers, using the inhalatory route, showed that some immunity could be produced by influenza virus adsorbed in this fashion, but the results were not decisive.¹⁵⁰⁻¹⁵³ Francis and his co-workers¹⁵⁴ found that experimental infection with type B virus did not give staunch protection four months later and noted elsewhere that the results obtained by this method were inferior to those obtained with subcutaneous vaccination.¹⁵⁵ Henle and his associates¹⁵⁶ have made essentially similar observations. On the other hand, McLean and his co-workers¹⁵⁷ have observed a striking contrast in the antibody response induced in swine by experimental infection, as compared to parenteral vaccination. Comparable groups of swine were infected and compared with groups given one, two or three doses of formalinized virus vaccine.

An arbitrary scale was devised to measure the presence and severity of the infection induced by subsequent intranasal challenge with active virus. This scale gave a "morbidity score" of 88.6 in non-immune unvaccinated control animals. The morbidity score for all vaccinated animals averaged 58.9, whereas animals recently recovered from a primary infection experienced a morbidity score of only 16.7. These results suggest that, at least in swine, the protection achieved for a short period by infection far exceeds that induced by use of vaccine. Whether these findings can be translated into human protection remains to be seen, certainly, one must acknowledge the possibility that immunization by the respiratory route has potentialities greater than those of the parenteral route. However, immunity resulting from infection is still type specific, experiments in ferrets have shown that recent recovery from influenza A does not in any way increase resistance to influenza B, and vice versa.¹⁵⁵

Reactions

The widespread use of influenza vaccine during the past two years has provided extensive evidence that untoward reactions to the vaccine are not infrequent and can be particularly severe in children. Reactions have varied from local tenderness and swelling to severe, almost explosive (but transitory) febrile responses resembling influenza itself. The mechanism of these reactions is not wholly clear. Influenza virus has been shown to be toxic for animals,¹⁵⁹⁻¹⁶¹ but this toxicity disappears with inactivation of the virus, such as in the standard preparation of vaccine. Yet the particular severity of the reactions in children^{142, 162-164} suggests that a toxic factor is involved. As pointed out by Dingle⁹⁵ and Salk,¹⁶⁵ the reactions in human beings may be due to a combination of both toxic and sensitization factors. Whatever their cause, they have been sufficiently frequent and severe to stimulate reconsideration of the customary dosage employed.^{142, 162-164} In comparisons of the reactions induced by different vaccine preparations, it appeared that reactions to calcium-phosphate-adsorbed vaccine¹⁴² or protamine-precipitated vaccine¹⁴² were apparently milder than those induced by the standard red-cell eluate vaccine. However, such differences may have been due merely to differences in the inherent potencies of the vaccines.¹⁶⁶ Salk,¹⁶⁵ in an extensive study, found a very close correlation between the amount of virus injected and the severity of reaction produced. He concludes that, since increases in amounts of antigen used do not yield corresponding increases in antibody titers, the optimum dose of influenza virus should be no greater than that which will be reasonably well tolerated. This suggestion admittedly rests on the assumption that antibody titers and resistance to clinical influenza infection

until later childhood where the need for decreasing the susceptibility to influenza by inoculation with influenza vaccine is indicated,¹⁰¹ and others called attention to the value of such immunization for the aged, in view of the well established evidence¹⁰⁵ that the mortality from influenza tends to be highest in this group. The major emphasis was laid on vaccination before anticipated epidemics, in view of the evidence that influenza A recurred fairly regularly on a cycle of two or three years, and influenza B at intervals of four to six years.¹⁰⁶ However, interepidemic outbreaks¹⁰⁷ and even isolated cases¹⁰⁸ have been reported, so that a justification existed for use of influenza vaccine in interepidemic periods. Accordingly, vaccination against influenza was widely practiced during the catarrhal seasons of 1945-1946 and 1946-1947, in children,¹⁰⁹ industrial groups,¹¹⁰⁻¹¹² schools and colleges¹¹³⁻¹¹⁷ and the general population. The vaccine used was composed half of Type B (Lee strain), and half of Type A (equal parts of PR8 and Weiss strains). The results observed during the influenza A outbreak of February and March, 1947, were, to say the least, disappointing. Attack rates in one group were 54 per cent in the vaccinated compared to 49 per cent in the unvaccinated¹¹⁴, three other paired groups showed 7.19 per cent against 8.09 per cent,¹¹⁵ 20.2 per cent against 27.8 per cent,¹¹⁶ and 9.5 per cent in both groups.¹¹⁷ It was readily demonstrated in these and other studies¹¹⁸⁻¹²⁰ that the virus strain responsible for this outbreak, now widely known as the FM-1 strain, was antigenically quite distinct from the standard Type A strains employed in the vaccine although it was definitely a variant of Type A. It appears likely that a similar or perhaps identical strain caused the 1946-1947 influenza outbreak in England,¹²¹ during which three paired groups exhibited attack rates, in vaccinated and unvaccinated subjects respectively, of 11 per cent against 21 per cent, 11 per cent against 17 per cent, and 7.1 per cent against 8.3 per cent — surprisingly comparable to the rates simultaneously observed in the United States.

A few months after it was isolated, strain FM-1 was incorporated into the standard vaccine preparations, replacing the Weiss strain, which in turn had been included previously because it represented the common variant of its time. This sequence of periodic and unpredictable shifts in the antigenic pattern of influenza A virus has aroused some caution in evaluating the usefulness of vaccination. This attitude is reflected in the conservative conclusions of the 1947 report of the American Public Health Association study commission on influenza vaccination⁹⁷ and also in an editorial, which states, "One can only conclude that as yet influenza vaccination is in its experimental stage, and its widespread uncontrolled use as a routine measure does not seem justified."¹²²

Factors Affecting the Efficacy of Influenza Vaccine

Numerous investigators have described antigenic variations in influenza A virus, and two strains were isolated during the 1943-1944 epidemic that were definitely variants from the standard "A" pattern.¹²³⁻¹²⁴ Such variations may become the major problem in making influenza immunization effective. The persistence of variant strains of Type A influenza during the winter of 1947-1948 has provided opportunity to assess the value of the FM-1 strain in the currently available vaccine. The results are hard to evaluate. Meiklejohn and Bruyn¹²⁵ found essentially no antibody response to a locally isolated variant strain, in the serums of persons immunized with vaccine containing the FM-1 strain. On the other hand, Salk and Suriano¹²⁶ observed a definite reduction in the incidence of acute respiratory illness in persons receiving the "new" vaccine as compared with a control group receiving the "old" vaccine. Meanwhile, the possibility that further strain variants will arise is constantly present, and it is in large part for this reason that "listening posts" for early detection of new strains or new outbreaks of influenza have been set up on a nationwide and world-wide basis.¹²⁷ However, it has been pointed out¹²⁴ that the antigenic range of protection achieved by immunization might be broadened if the average antibody titer induced by the vaccine could be increased, since a rise in the titer to the homologous strain usually carries with it a comparable rise in the titers against related strains. Several possible methods of achieving the increase in titer have been explored. The simplest appears to be to concentrate the virus antigen. This has been effectively accomplished by centrifugation¹²⁸ and by alcohol precipitation,¹²⁹ both methods being designed primarily for purification, but yielding high concentrations of virus elementary bodies. It is indeed possible to increase the antibody response by increasing the dose of antigen,¹³⁰ but the gain is small in proportion to the stimulus applied, several workers having reported that a tenfold increase in the amount of antigen used gives an increase of only about two to two and a half times in antibody rise obtained.¹³¹⁻¹³³

Repeated inoculations of vaccine would ordinarily be expected to raise the antibody level above that obtained with one injection, were the response to influenza vaccine similar to that observed with diphtheria and tetanus toxoids and most other antigens. Although such increases in antibody titer have been observed in swine after repeat injections of swine influenza vaccine,¹³⁴ this has not been borne out in human experiments.¹³²⁻¹³⁵⁻¹³⁶ The extensive studies of Beard and his associates¹³⁷ in swine, however, suggest that the difference between success and failure may depend upon the interval between doses.

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are generally closely correlated. It conflicts with the findings of Hare et al.,¹⁶⁷ who concluded that the antibody response was inadequate after anything less than a full dose of vaccine.

Considerable alarm has been expressed over the danger of true allergic reactions from inoculation of influenza vaccine, which is derived from the chorioallantoic fluid of the infected chick embryo. Two fatal reactions are reported to have occurred, in both of which a history of sensitivity to eggs was later traced. The apparently alarming possibilities inherent in the administration of egg proteins to a large number of human beings were reviewed by Ratner and Untracht,¹⁶⁸ who collected evidence suggesting that the problem was a widespread one. The report by Curphey,¹⁶⁹ of a death—said to have been allergic in nature—in a small child a few hours after an injection of influenza vaccine, and a similar report elsewhere¹⁷⁰ provided a basis for renewed caution in administering the vaccine. It is generally agreed that a history of possible sensitivity to egg protein should be carefully sought for, however, it is on record¹⁷¹ that many injections of vaccine have been given, without reaction, to persons with histories of mild egg sensitivity. A recent editorial¹⁷² has restated the widespread opinion that the risk of this type of reaction—slight as it is—might be reduced by further purification of the virus by the centrifuge¹⁷⁸ or alcohol¹⁷⁹ methods, thus eliminating most of the extraneous egg protein. However, a re-examination of the death reported by Curphey¹⁶⁹ suggests—as Salk¹⁷³ has pointed out—that it was due to a toxic rather than an allergic reaction. If such toxic deaths can indeed occur, the use of purified vaccines must be tempered with a caution against employing excessive quantities of virus, since the incidence of reactions rises sharply within a relatively narrow range of increase in virus concentration.¹⁶⁵

(To be continued)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35271

PRESENTATION OF CASE

A forty-nine-year-old male cook was admitted to the hospital because of weakness, cough, chills and chest pain.

Six days before admission the patient noticed excessive fatigue. On the following day he developed anorexia, headache, dryness of the mouth, a light cough productive of whitish sputum with brownish streaks, and pain in the right anterior chest made worse by breathing. Four days before admission he had several shaking chills and the next day fatigue increased markedly. He developed pleuritic pains in the left anterior chest and had profuse sweats after ingestion of "red pills" that had been suggested by a druggist. Two days before admission the chest pain diminished, but over the following two days the cough became much worse, and since the day before admission the sputum had been streaked with red blood.

At twelve years of age he had had rheumatic fever and had been kept in bed for seventeen days. At twenty-one he had recurrent joint involvement after an upper respiratory infection. After he had recovered he had a tonsillectomy. For the past eighteen years his hip joints had bothered him intermittently, especially with weather changes. Sixteen months before admission he had seen several physicians because of easy fatigability, exertional dyspnea and occasional dyspnea at rest, and a slight cough. He was given digitalis and advised to reduce his activities. Two months later he was admitted to another hospital, where x-ray examination revealed an enlarged heart. He was advised to rest and to continue taking digitalis. He had never had ankle edema and no definite orthopnea. He had had gonorrhea five times between fourteen and twenty-four years before admission. On each occasion he was promptly treated and cured.

Physical examination revealed a well developed, well nourished, dyspneic man who appeared feverish and flushed. The skin was hot and moist. The tongue was coated and dry, and the throat red. The chest appeared normal, with good expansion. There were crackling rales, diminished breath sounds, and slight dullness to percussion in the right infrascapular area and over the right base posteriorly. The heart showed completely irregular rhythm with an apical rate of 104 and a radial pulse of 92. There were a Grade II apical systolic murmur and an apical mid-diastolic rumble. The left border of the heart appeared in normal position. The extremities were normal.

The temperature was 105°F, and the respirations 30. The blood pressure was 135 systolic, 55 diastolic.

Examination of the blood showed a red-cell count of 4,600,000 and a white-cell count of 6400, with



FIGURE 1

89 per cent neutrophils, 7 per cent lymphocytes and 4 per cent monocytes. The urinary sediment contained 2 to 5 red cells and 4 to 6 white cells per high-power field and occasional granular casts. A stool was normal. Sputum smears showed a few gram-positive streptococci. Repeated smears were negative for tubercle bacilli. The sputum culture showed no pneumococci.

An x-ray film of the chest (Fig. 1) showed mottled increased density occupying the whole upper half of the right-lung field and appearing to include only the right upper lobe. The hilar markings were slightly increased. The heart was prominent in the region of the left auricle and there was a prominence of the pulmonary artery.

The temperature continued at 103 to 104°F, and the respirations slowly rose over three days to a rate of 50. He was continued on digitalis and penicillin until the fourth day, when sulfadiazine was substituted for penicillin. A roentgenogram on the third day showed extension of the density to the right lower lobe and also involvement of the left lung (Fig 2). On the fourth day the respirations became more labored and rapid, and cyanosis and dyspnea increased. The lungs filled with coarse rhonchi, and large amounts of bright-red sputum



FIGURE 2

were raised. Early on the fifth day the respirations became very shallow, and the patient died.

DIFFERENTIAL DIAGNOSIS

DR ALLEN G. BRAILEY: I should like to see the x-ray films.

DR MILFORD D. SCHULZ: This first film was taken prior to the illness, it antedates it by three months and shows normal lungs. The heart is enlarged in the region of the left auricle. Films made at the time of hospital entry show a mottled area of increased density occupying the major portion of the right upper lobe that in two days extended to the lower right chest, and there is also involvement of the left chest. The mottling has become quite confluent. The lung roots are larger on the films made at the time of the illness than before, but at no time is there evidence of fluid in either pleural sinus.

DR BRAILEY: Would you make a diagnosis of rapidly advancing pneumonia from that picture?

DR SCHULZ: Yes, or pulmonary edema. If one saw the last film only, one would be tempted to think that it was pulmonary edema, especially in the face of the mitral disease.

DR BRAILEY: The significant features of this history are that a middle-aged cook with long-standing rheumatic heart disease died after eleven days of an acute febrile illness with symptoms largely confined to his chest. The causes of death that need to be seriously considered are acute fulminating tuberculosis, pneumonia of some type—perhaps embolic—and acute rheumatic infection. The bloodspitting and the x-ray appearance of his lungs make it desirable to mention tumor and bronchiectasis also, but these seem to be excluded by the acute febrile course. Certainly, if present, they must have been complicated by severe secondary infection.

It is obvious from the protocol that tuberculosis was seriously considered by the medical service. However, very rarely does tuberculosis, even in an explosive, pneumonic form, kill in so short a time. On the other hand, it might be argued that this man had a seriously damaged heart, which served to hasten his death. It is reported that repeated smears of sputum failed to show tubercle bacilli. This is a major point against the diagnosis but does not rule out the possibility. This man had had symptoms referable to his heart for many years, and he must have had previous x-ray examinations of his chest. Yet there is no mention that tuberculous lesions had ever been observed prior to his present illness. It is very unusual for tuberculosis to arise *de novo* in a man of forty-nine who has shown no x-ray evidence of previous infection. I cannot exclude tuberculosis, but I very much doubt if that will prove to be the anatomical diagnosis.

The diagnosis of pneumonia is not so easily disposed of. It is obvious that he had a pneumonic process of some kind in his chest, and his whole physical course is not inconsistent with pneumonia due to pneumococci or one of the other pyogenic organisms. The polymorphonuclear percentage is increased, and the low total white-cell count may only be a commentary on the severity of his infection. However, one should have no particular difficulty in finding and isolating the offending organism in pyogenic pneumonia, whereas we are told that pneumococci could not be grown from the sputum and only a few gram-positive streptococci were seen. Furthermore, most of the organisms that may provoke a fatal pneumonia are quite susceptible to adequate treatment with penicillin or sulfadiazine. Yet these agents were of no value to this patient. There are forms of pneumonia, very exotic in this locality, that could have produced this picture—such as melioidosis and pneumonias due to some of the rickettsias and coccidiomycetes. However, these conditions are so rare

in New England as to deserve hardly more than passing mention

His cough, his marked bloodspitting and his increasing dyspnea and cyanosis are all consistent enough with repeated pulmonary infarctions. But if he had a shower of pulmonary emboli, where did it come from? We are given no hint of phlebitis of any peripheral veins, although we know from sad experience that the source of emboli is often not recognized during life. His auricles were fibrillating, and the formation of thrombi in the auricles is a fairly common and dreaded complication of such fibrillation. It is quite possible that he developed a thrombus of the right auricle or appendage, which then shed emboli from time to time to plug branches of the pulmonary arteries. But it would be very remarkable, indeed, if these emboli all elected to lodge in the artery to the right upper lobe as the x-ray report suggests. And what about his fever? I think pulmonary infarction would scarcely give rise to temperatures of 103, and certainly not to 105°F, unless the emboli involved were infected. But septic emboli from the heart imply an acute bacterial endocarditis involving the tricuspid valve, and of such a rare lesion we have no hint. I cannot exclude the possibility, but I doubt if this man died of pulmonary embolism.

Finally, there exists the possibility that this man died of acute rheumatic fever and its complications. The literature contains a number of contributions purporting to show that rheumatic infection may, of itself, produce a pneumonitis distinguishable from other forms of pneumonia and from chronic passive congestion. There is as yet no general agreement that such an entity exists, but neither can the evidence be brushed easily aside. Those interested in the subject may well begin with a scholarly paper by J. R. Paul¹ and a more recent review by Seldin et al.² These, and other authors, point to a group of patients with a history of manifest rheumatic infection who are struck down with an illness of sudden onset, a temperature often of high level, a hacking cough, bloody sputum, marked dyspnea and cyanosis and usually a fatal outcome within ten to fourteen days. Onset with chills is rare. There may be transient pleurisy; physical signs of lung involvement are often minimal. The white-cell count is usually high (as it was not in the subject of this discussion). X-ray study may show involvement of one or of several lobes. Often, there is little to distinguish the x-ray picture from that of chronic passive congestion. Study of the sputum reveals no significant organisms and usually little pus. Frequently, the evidence of cardiac failure, as in our present case, is not impressive. The venous pressure and circulation time may be very little elevated, and the pulse rate and blood pressure may be well maintained. At post-mortem examination, the outstanding features appear to be the mononuclear and frankly hemorrhagic charac-

ter of the alveolar exudate, and attention is also called to a hyaline membrane lining the smaller bronchioles.

Whether these are features worthy to identify a separate clinical entity must lie outside this discussion. But it must be conceded that there are persons with a long-standing history of rheumatic infection who die as this man died — after a brief but stormy illness characterized by fever, cough, hemoptysis, rapidly increasing dyspnea, orthopnea and cyanosis with little evidence of heart failure but with evidence of a pneumonic process for which there is no readily apparent cause.

CLINICAL DIAGNOSES

Pneumonia, fulminating, ? etiology
Rheumatic heart disease, with mitral stenosis

DR BRAILEY'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis
and auricular fibrillation
Acute rheumatic fever
Rheumatic pneumonia?

ANATOMICAL DIAGNOSES

Atypical viral pneumonia, fulminating
Rheumatic heart disease, with mitral stenosis

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN Autopsy showed rheumatic heart disease involving both the aortic and mitral valves, with a moderate degree of stenosis of the mitral valve. There was no evidence of superimposed bacterial endocarditis or of acute rheumatic endocarditis. The lungs were the interesting feature of this case. They were tremendous in size, the right lung weighing 2000 gm and the left, 1300 gm. Whenever one sees a lung weighing 2000 gm the first thing to think of is lobar pneumonia. On the other hand this did not look like lobar pneumonia. The cut surface revealed a spotty granularity and was extremely hemorrhagic. The right upper lobe was entirely consolidated, and the middle and lower lobes to a lesser degree. In the left lung the process was limited to a large area near the hilus involving a third to a half of each lobe. We cultured them and were unable to get any pneumococci or streptococci. We thought immediately of the fulminating influenza-virus pneumonia or rheumatic pneumonia.

Microscopical sections showed fairly acute pneumonia, bronchitis and interstitial pneumonitis, a condition that has been described in atypical viral pneumonia.^{3,4} There was infiltration of the alveolar walls as well as the alveoli themselves, more particularly around the bronchi, with polymorphonuclear leukocytes, fibrin and monocytes. The bronchioles were filled with organizing exudate. The atria and a large number of the alveoli were filled with blood, which was probably a secondary manifestation. The picture closely resembles sec-

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and a quarter years. Two and a half years before admission, an x-ray film showed a shadow in the left upper lobe, and three months prior to admission a survey film confirmed the findings of the previous examination. That is of extreme importance. Apparently, there was no change over something more than two years. The right-angle telescopic lens was used in the upper lobes, and all we have is a visual report. So we do not know whether the mass was fixed or not, but it was round and smooth, seemed to be in two lobules and seemed to obstruct the bronchus completely. I assume that the collapsed area in the left upper lobe is the portion of the upper lobe that would be aerated through the bronchus that was obstructed by the visualized mass. Is that reasonable, Dr. Hanelin?

DR. HANELIN: I think the whole left upper lobe is reduced somewhat. It may be that the apical division is less aerated than the remainder.

DR. PITTMAN: We have a report of complete obstruction with no air in or out of it.

DR. HANELIN: It is possible, although unlikely, that the entire lobe is represented by the density that we see at the apex, the remainder of the lung being aerated by the lower lobe. The major fissure is not well demarcated.

DR. PITTMAN: Physical examination is not very helpful in this case. There are signs of some diminished tactile fremitus and occasional rales over the right-upper-lobe area, and I suppose that means the extreme upper chest. The diastolic pressure was high, with a nonenlarged heart, I cannot relate it to anything. The liver edge was two finger-breadths below the costal margin and fairly low. I doubt whether that is significant enlargement, and I assume that the rubbery prostate, which was three times the normal size, represented benign hypertrophy.

The blood on examination was fairly good with a hemoglobin of 12.5 gm. The white-cell count of 20,000, I assume, was a reflection of some infection in the lung. No sputum examination is noted. That is the story. He had been examined on the outside and following bronchoscopy came in for operation.

What was believed to be the matter and what was the preoperative diagnosis? If we go back to the very first line of this abstract it is stated that the patient was a wool spinner, and I think that means that one should stop and consider what particular things wool spinners might have. They might have dust carried in with the material they were spinning, although that gives an entirely different diffuse, bilateral picture and I do not think dust was important in this case. I suppose one must mention in the discussion of a patient who works with wool what we were taught in our youth about anthrax, it gives a pneumonic type of process and is acutely fatal. I believe that we do not have to consider it here.

From reading the record possibly one should give consideration to a foreign body that had been in

the bronchus for a long time and had become covered with tissue. I think that that is extremely far-fetched. One should have more sepsis. The fact that there is no history does not rule it out, but in a man of this age it makes it much less likely.

Then we come down, obviously, to a new growth, because here is a mass that occluded the lumen of a bronchus. First to consider is a malignant new growth. There had been no change in this man's x-ray films as far as we can tell for something over

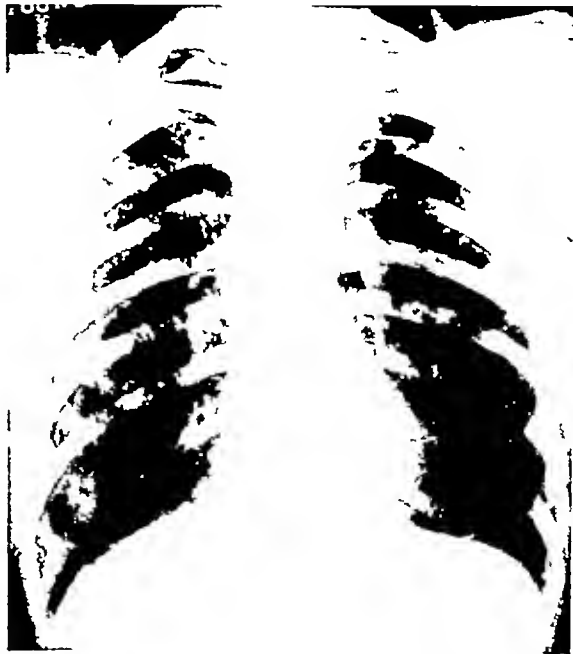


FIGURE 1

two years. I cannot conceive of a bronchial carcinoma not progressing over a two-year period. In addition, this was a round, smooth mass. We do not know about fixation because it could not be touched. It was quite removed from the carina, but there was no widening or fixation of the carina, and if some lesion of that type had been present for over two years, it seems to me, there would have been extension that would have changed the appearance of the carina.

That brings me down to a benign intrabronchial lesion, which seems to me to fit this story best. The patient had nonspecific bronchial trouble. Probably, he had a good deal of blood streaking, which is extremely common in these tumors. He was not invalidated by his disease. Two and a half years or three years before admission he had enough trouble so that an x-ray film was taken but not enough trouble so that he was willing to follow advice, because as a result of the x-ray findings he was told that he should be hospitalized. He probably was not very sick. It seems to me that in a sixty-two-

tions that I found in our files of the old influenza epidemic of 1918, where the lungs were hemorrhagic and wet as these were. It is one of the few cases of atypical viral pneumonia that we have seen. Unfortunately, we did not have viral studies done on the material, so that we do not have actual proof of the diagnosis. There was 500 cc of fluid in the right pleural cavity at the time of autopsy, and a little under 100 cc on the left side.

DR BRAILEY: Were there any Aschoff bodies in the heart?

DR CASTLEMAN: No. We did consider rheumatic pneumonia, since this patient had a history of rheumatic infection. In rheumatic pneumonia as a rule one does not see so much cellular reaction, but rather a great many phagocytes and red cells. Also, the bronchi are usually not filled as these were. Of course, the whole question of rheumatic pneumonia is still a moot subject.

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3. Parker F. Jr., Jolliffe L. S., Barnes M. W. and Finland M. Pathologic findings in lungs of five cases from which influenza virus was isolated. *Am J Path* 21:797-819 1946.
4. Parker F. Jr., Jolliffe L. S. and Finland M. Primary atypical pneumonia. *Arch Path* 44:581-608 1947.

CASE 35272

PRESENTATION OF CASE

A sixty-two-year-old man, a wool spinner, entered the hospital because of hemoptysis.

For many years the patient had had "bronchial trouble," with cough, gradually increasing dyspnea and occasional blood-streaked sputum for three years. Two and a half years prior to admission an x-ray film revealed a shadow in the left upper lobe, and hospitalization for further study was advised. Instead he resorted to "heat treatments," with some improvement. Three months prior to admission an x-ray film taken in the course of a mass survey confirmed the findings on the previous examination, and a bronchoscopy was performed, with some alleviation of the cough but with aggravation of the hemoptysis. On bronchoscopy the trachea was deviated slightly to the right, as if from extrinsic pressure on the left side, the carina was in the midline, with no widening or fixation. The orifice of the left upper lobe, visualized through the right-angle telescopic lens, appeared to be completely occluded by a rounded, smooth mass, which seemed to be in two lobules. No air was seen to be passing in or out of the orifice. There was some reddening of the left main bronchus and left-lower-lobe bronchus. Following bronchoscopy the patient was scheduled for hospitalization.

On physical examination diminished tactile fremitus was present over the left upper lobe posteriorly, and occasional rales were heard over this area. The heart was not enlarged. The liver edge was palpable two fingerbreadths below the costal

margin. The prostate was enlarged to three times the normal size and was "rubbery."

The blood pressure was 180 systolic, 120 diastolic. Examination of the blood showed 12.5 gm of hemoglobin, with a white-cell count of 20,000. The specific gravity of the urine was 1.020, no albumin, sugar or acetone was present. The serum protein was 7 gm, and the nonprotein nitrogen was 36 mg per 100 cc. The prothrombin time was normal. An x-ray film of the chest, with fluoroscopy and a barium swallow, showed elevation of the left hilus, with some increased density of the left apex medially. There was a 1-cm, rounded area of density in the left first interspace anteriorly. The left upper lobe was decreased about a third in size (Fig 1). Elsewhere, the lung fields appeared clear. There was no evidence of pleural fluid. The esophagus was slightly deviated to the left at the level of the suprasternal notch. Just above this area there appeared to be slight compression of the trachea from the right, it was likewise slightly deviated to the left.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR HELEN S. PITTMAN: I hope Dr Hanelin is going to help me on this x-ray report. It confuses me. I wonder if we may see the films now.

DR JOSEPH HANELIN: These are spot films that show a part of the esophagus and also show the trachea quite well. I do not believe that the course of the esophagus, above the aortic arch, is particularly unusual. All the films of the chest were taken at the same time, or a day apart. I think the finding of greatest importance is evidence of collapse of the left upper lobe. The left hilus is elevated. There is diffuse increased density in the region of the apex, and there is an irregular area of density, about 1 cm in size, in the left first interspace. The esophagus and the trachea below the level of the arch are only questionably abnormal. It is possible that there is a greater degree of indentation along the left aspects of these structures, but I cannot be sure of it. The lungs elsewhere are clear. The heart is not enlarged. The aorta is elongated and tortuous.

DR PITTMAN: Is there any special compression of the trachea from the right?

DR HANELIN: The trachea follows a somewhat tortuous course. If this were to result from extrinsic pressure, the adjacent mass would be of most unusual contour.

DR PITTMAN: Then I am going to forget about it, because I do not know anything else to do about it that makes any sense.

The points that seem to me of interest and importance in this history are that this man, who had cough, increasing dyspnea and occasional blood-streaked sputum for years and who had an intra-bronchial mass, gave no history of ever having had a wheeze. He must have had a wheeze. There had apparently been no change over a period of two

Castration is one of the conditions of release of incorrigible male sex offenders (who as a civilized refinement, are refurnished with glass testicles), just as numbers of the inmates of mental-deficiency institutions have been sterilized before release.

year-old man, with a rather long history, minimal symptoms, repeated though apparently not very important hemoptysis, and in reasonably good health, the most logical explanation is a benign adenoma in the bronchus, the parenchymal lung disease representing collapse distal to the mechanical obstruction. I shall therefore make that my diagnosis.

DR DONALD S. KING: At one time it was believed that adenoma occurs more frequently in females than males. Dr. Ronald Sniffen has been working on these patients, and I think he has found the sex incidence to be about fifty-fifty.

DR PITTMAN: It still is that way in the literature—more frequent in females.

DR KING: But not in our series here.

DR PITTMAN: It also occurs in a slightly younger group than sixty-two years.

DR KING: I cannot remember having seen an adenoma in a man of sixty-two. We have also had epidermoid carcinomas recently that have hung on for a long time. I know the answer, but I agree that it seems as if this man was fairly well to have had a carcinoma.

DR J. G. SCANNELL: We arrived at the same point that Dr. Pittman did. We thought that the patient had a benign lesion of the bronchus, although we also considered carcinoma of the lung. In a man of sixty-two we decided to do a lobectomy, preserving as much lung as we could. At operation the tumor mass presented in the main left-upper-lobe bronchus, which was extremely short. It was therefore necessary to go closely around the tumor, leaving almost no free margin. The patient was dyspneic, and because of his age, unless there was an out-and-out malignant tumor, we believed that a pneumonectomy was not justified and relied on the benign character of an adenoma. I have forgotten whether or not we had a biopsy before operation.

DR TRACY B. MALLORY: Dr. Castleman did a frozen section during the operation, and I believe he reported adenoma.

DR HANELIN: How much was the left upper lobe reduced in size?

DR SCANNELL: It was not particularly reduced in size. The operative note says that the chest was opened, disclosing a somewhat collapsed left upper lobe, collapsed chiefly in the apical posterior segment.

CLINICAL DIAGNOSIS

Pulmonary tuberculosis

DR PITTMAN'S DIAGNOSES

Benign adenoma, left-upper-lobe bronchus

Collapse of left upper lobe, with chronic infection

ANATOMICAL DIAGNOSIS

Bronchial adenoma

PATHOLOGICAL DISCUSSION

DR MALLORY: The specimen we received in the laboratory showed an intrabronchial tumor. It was, as predicted, a benign adenoma, which had extended through the tracheal wall. Dr. Scannell, in his operative note, said it was shaped like a collar button, which is a common picture presented by this type of tumor. The upper segment of the lobe showed very extensive dense fibrosis, evidently the result of old organization of a pneumonitis. All the anatomical structures in that area had been rather thoroughly destroyed. The rest of the lobe was small and slightly collapsed.

DR PITTMAN: That probably was represented by the dense area on the film?

DR HANELIN: Yes.

DR MAHLON HOAGLAND: Would a tuberculoma be likely to produce such a picture?

DR PITTMAN: I have spent a good deal of time in the Treadwell Library, since I received this abstract, trying to find an intrabronchial tuberculoma but did not succeed. That is all I can say. That is why I did not mention it in my discussion.

DR SCANNELL: Have we had bronchial adenoma with satellite metastatic lymph nodes?

DR MALLORY: We have had only 1 in our series of cases and we have seen 1 or 2 specimens sent in from elsewhere in which satellite lymph nodes were involved, but never a case with generalized metastasis, although they have been reported in cases in which there is no reason to question the diagnosis.

DR HOAGLAND: Were any lymph nodes removed with this specimen?

DR MALLORY: Yes, but they were anthracotic and did not contain tumor.

DR SCANNELL: The term "adenoma" has bothered me because as I understand it, it is not a gland-forming tumor—just a pseudo-adenoma really.

DR MALLORY: This present tumor resembled a true adenoma, however, rather more than some do. There were in a few areas cells producing mucin, which is an unusual phenomenon, but I still believe there is no doubt that it should be classified as a benign tumor. The most characteristic of these tumors resemble very closely the histologic structure of carcinoid tumors of the appendix and small intestine. The majority of carcinoids remain localized, a few involve regional lymph nodes, and a very small proportion metastasize. Generally both tumors share this characteristic low grade of malignancy. A second group of tumors likewise usually classed as bronchial adenomas have the histologic features of some of the better differentiated basal-cell tumors of the skin.

ing or deceased partner to the remaining partners" Provision is made for partners who originally staved out of the Service because of the lack of these new safeguards, to join it for the first two months after the passage of the Bill and receive compensation for the good will of their practices

Various other amendments to the Act give substance to the promises that had been made—promises that last year were instrumental in finally inducing a majority of the medical profession to accept the terms of employment established under the Act

There have been many warnings regarding the harm that British physicians believe medical practice has suffered as a result of the Act. The Amending Bill appears as evidence of good faith on the part of the Ministry to make the practice of medicine as acceptable as possible to all who are concerned with it. The *British Medical Journal*, mouthpiece of the British Medical Association, takes a somewhat different attitude. Many more matters were to have been included in the Amending Bill, and in their omission the Minister has failed to fulfil his promise to discuss their inclusion with the medical profession. "He has again committed a breach of trust," the *Journal* insists, "with a profession that has loyally collaborated with the Government in operating a Service full of imperfections." A final answer cannot yet be given to the question whether governmental control of medicine can in any way be made compatible with reasonable efficiency and economy

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- 1 Leading Article. Amending bill. *Lancet* 1 873 1949
- 2 Leading Article. Amending bill. *Brit M J* 1 904 1949

IN HOC SIGNO

THE leopard, according to a remote biologic authority, can no more change his spots than can the Ethiopian his skin. The allusion, however, put originally in the form of a question, applies only to the individual and to a pre-Darwinian concept of the nature of things, change is inherent in all life and that form of life can survive the longest that can best adapt itself to its changing environment

So it is with journalism, which, like lava, frequently the result of an explosive eruption, must remain fluid if it expects to get anywhere

The *New England Journal of Medicine*, as a familiar example, has changed a number of its spots in its hundred-odd years of existence. Its changes have been gradual, however, as considered changes should be, perhaps its progress may be likened to that of a glacier rather than a stream of lava, and certainly the melting glacier gives off many streams of water whereas the lava carries only destruction in its teeth

In the files of the *Journal* a distinguished ancestry lies preserved. The *New England Journal of Medicine and Surgery and the Collateral Branches of Science*, "Conducted by a Number of Physicians," was first proposed by Dr John Collins Warren and made its initial appearance in January, 1812, the leading article consisting of "Remarks on Angina Pectoris" by John Warren

In 1823 *The Boston Medical Intelligencer*, a weekly publication, appeared, conducted by Jerome V C Smith. It contained "Extracts from Foreign and American Journals, A Variety of Local Intelligence on Subjects Connected with Medicine, Biographical Sketches of Distinguished Surgeons and Physicians, Descriptions of the Principal Hospitals in Europe, Original Articles on Various Diseases, with Concise Views of the Improvements and Discoveries in the Medico-Chirurgical Sciences"

The charms of the *Intelligencer* completely overcame the *New England Journal of Medicine and Surgery*. After a short courtship they were united in February, 1828, the synchronous result of the union being the *Boston Medical and Surgical Journal*, born on the nineteenth day of the same month

Many changes in type, format and substance, but never a lapse in virtue, marked the peaceful, century-long progress of the *Boston Medical and Surgical Journal*. Of these changes the latest were its acquisition by the Massachusetts Medical Society in 1921, and the assumption of its present title in 1928. The *New England Journal of Medicine* has itself undergone conservative changes. The type has been improved, both of the text and of the title. The cover has gone mildly into the red, even if only on alternate weeks. Other minor alterations have

not for eugenic reasons but in order that they may re-enter society without increasing society's burdens

In view of the exposé of current penal methods that has been revealed to the citizens of Massachusetts in recent months, the penal code of Denmark has much to recommend it

STRANGE BEDFELLOWS

BRITAIN'S "most noted radiologist," according to Bulletin No 429 of the Citizens Medical Reference Bureau Inc, of 1860 Broadway, New York City, is opposed to mass x-ray checkups. In the words of Dr James F Brailsford, founder of the British Radiological Association and director of the x-ray and radium departments at Birmingham Hospital, as reprinted from the Los Angeles *Times*:

If you feel fit and well, stay away from all doctors. Even in the case of cancer, nature will notify educated persons when to seek medical advice. Mass x-ray examinations for tuberculosis and cancer do more harm than good. Periodic examinations of those who have no symptoms of tuberculosis and cancer are of doubtful value.

"Most people know it when they have cancer," according to Dr Brailsford's novel creed. "The trouble is that even doctors, knowing they have cancer, keep quiet until too late. However, if people will seek advice when they feel sick and not worry when they feel well, lives, money and time will be saved."

The distinguished visitor from Great Britain, who expressed his views as quoted above to a group of physicians at the Hollywood Presbyterian Hospital, is undeniably entitled to his own opinions and the right to express them. It is unfortunate, however, that opinions so contrary to those held by the majority of conscientious physicians should receive any widespread publicity.

The secretary of the Citizens Medical Reference Bureau, Inc, which has so quickly rallied to Dr Brailsford's unique standard, states, in reply to a request for information, that this organization is a lay one, having for its purpose, "To preserve, establish, maintain and safeguard through publicity and other lawful means, the right of adults or, in the case of minors, the right of parents or guardians to determine the form or manner of treatment or

care to be prescribed or applied for the cure or prevention of disease."

Certain of the objectives of the Citizens Medical Reference Bureau are undoubtedly praiseworthy. Where it loses its perspective and departs from its apparently laudable purpose is in maintaining for a primary object not the protection of the rights of the majority to enjoy, so far as possible, freedom from exposure to disease, but what it considers to be the right of the individual to escape vaccination and any other compulsory measures that are designed to prevent him from becoming a menace to the public. What citizens of this type invariably fail to understand is the necessity, in a working democracy, for all members of society to surrender certain personal liberties the exercise of which may jeopardize the common good.

The members of Citizens Medical Bureau, Inc, like those friendly foes of medical practice, the Christian Scientists, happen at the moment to be aligned with the medical profession in its opposition to compulsory health insurance.

Politics makes strange bedfellows, even if only for a night.

GREAT BRITAIN'S AMENDING BILL

ENGLAND'S Minister of Health has submitted to Parliament his promised bill for amending the National Health Service Acts of 1946 and 1947. "Let it be said at once," the *Lancet*¹ reports, "that the Minister has fully kept faith, for all the promises made a year ago are here translated into legal form."

The manner in which a general practitioner may be remunerated is safeguarded by a clause that makes it impossible to change this remuneration by regulation and to make it consist wholly or mainly of a fixed salary without reference to the number of patients for whom he has agreed to provide services. Clause 11 bans any requirement that all specialists employed for the purpose of hospital and specialist services shall be employed whole time.

The position of partnerships and the transfer of practices is clarified, "and appropriate methods are provided for transferring the share of a partner-

Meningitis, undetermined, was reported from Arlington, 1, Brockton, 1, Taunton, 1, total 3
 Polioencephalitis was reported from Arlington, 1, Braintree 1, Brookline, 1, Cambridge, 1, Milton, 4, Newbury, 1 Wareham, 1, total, 10
 Salmonellosis was reported from Leominster, 1 Peabody 1 total, 2
 Septic sore throat was reported from Boston, 2 Lynn, 1, Worcester, 1, total, 4
 Typhoid fever was reported from East Longmeadow, 1 Everett, 2, Leominster, 1 Peabody, 1 Somerville 1 total, 6
 Typhus fever was reported from Boston 1, total, 1
 Undulant fever was reported from Buxboro, 1 Maynard 1 Natick, 1, Pepperell, 1, total, 4

MISCELLANY

BOSTON UNIVERSITY ORGANIZES DEPARTMENT OF LEGAL MEDICINE

Dr Walter Jetter, pathologist for the Massachusetts Department of Mental Health and assistant professor of legal medicine at Harvard Medical School, has been selected by the trustees of Boston University to head a new department of legal medicine at Boston University School of Medicine. He will assume his new duties on July 1.

Dr Jetter was born in Buffalo, New York, on September 4, 1905. He received his M.D. degree from the University of Buffalo School of Medicine in 1931 and his M.S. in medicine in 1938 from the same school.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Ärztliche Rheokardiographie By Wolfgang Holzer and Kurt Polzer. 8° paper, 144 pp., with 88 illustrations and 3 tables. Vienna: Verlag Wilhelm Maudrich, 1948. \$5.00. *Bücher der physikalischen Medizin*. Volume III.

This monograph is comprehensive in scope, discussing the method in general, animal experimentation and the normal rheocardiogram in man, and in diseased conditions of the heart. The pertinent literature is noted throughout the text, which is concluded with an extensive bibliography of sources mentioned in the text and dating to 1947. There is a good index. The material is well arranged. The monograph is well published in a typical German style. It should be available to all persons interested in cardiology.

Bacterial and Mycotic Infections of Man. Edited by Rene J. Dubos, Ph.D., The Rockefeller Institute for Medical Research. 4° cloth, 785 pp., with 101 illustrations, including 3 plates in color. Philadelphia: J. B. Lippincott Company, 1948. \$5.00.

This comprehensive treatise on medical bacteriology is a companion volume to *Viral and Rickettsial Infections of Man*, edited by Dr. Thomas M. Rivers and published by Lippincott in 1948. Thirty-four authors collaborated in the production of the volume. The beginning chapters deal with general principles and are followed by discussions of the various bacteria, spirochetes and mycoses. The concluding chapters are devoted to sterilization, chemotherapy, epidemiology and the cultivation and identification of pathogenic bacteria. The material is well arranged. There are lists of selected references appended to the various chapters. The text is concluded with comprehensive indexes of authors and subjects. The book is well published but since it weighs nearly 5 pounds a lighter paper, if possible, should have been used. This should be considered an essential reference book for all medical libraries and should be available to all persons interested in bacteriology and bacterial diseases.

The Digestive Tract in Roentgenology. By Jacob Buckstein, M.D., assistant professor of clinical medicine, Cornell University Medical College, visiting roentgenologist (alimentary-tract division), Bellevue Hospital, New York City, attending gastroenterologist, Beth David Hospital, New York City, and consultant in gastroenterology, Central Islip State Hospital, New York. 4° cloth, 889 pp., with 1030 illustrations. Philadelphia: J. B. Lippincott Company, 1948. \$16.00.

This treatise is based on the author's experience of twenty-five years at Bellevue Hospital, where an enormous amount of material was available, and also on his private practice as a gastroenterologist. The material is well arranged. Selected lists of references are appended to the various chapters. The pertinent literature is reviewed in each special chapter. Indexes of authors and of subjects are referred to throughout the text. The volume is well published and is recommended as a standard reference work for all medical libraries and to all roentgenologists.

Viral Diseases of Man. By C. E. van Rooven, M.D., D.Sc. (Edin.), M.R.C.P. (Lond.), research member and professor of virus infections, Connaught Medical Research Laboratories and School of Hygiene, University of Toronto, and A. J. Rhodes, M.D., F.R.C.P. (Edin.), research associate and professor of virus infections, Connaught Medical Research Laboratories and School of Hygiene, University of Toronto and consultant in virus infections, Hospital for Sick Children, Toronto. 8° cloth, 1202 pp., with 43 illustrations. New York: Thomas Nelson and Sons, 1948. \$22.50.

This edition of a standard reference work first published in 1940 has been thoroughly revised in the light of the knowledge of the subject gained during the past ten years. The literature has been surveyed through 1947 with the addition of some papers published during the early months of 1948. Selected references are appended to each chapter. The latest information on two diseases prevalent in the United States—influenza and poliomyelitis—is given at length. All the diseases now attributed to viruses are discussed in detail. The type and printing are good but the use of a coated paper making the volume weigh more than 5 pounds is not justified by the few illustrations. The book should be in all medical libraries and should be available to all general practitioners.

The Common Sense Psychiatry of Dr. Adolf Meyer. Fifty-two selected papers edited with biographical narrative by Alfred Lief. 8° cloth, 677 pp. New York: McGraw-Hill Book Company, Inc., 1948. \$6.50.

This volume constitutes a collection of fifty-two papers of Dr. Meyer brought together from scattered sources and reprinted in one volume for convenience for reference purposes. A short biographic sketch precedes the papers. A glossary and an index conclude the volume. The publishing is excellent. The book is recommended for all medical libraries and should be available to all psychiatrists.

Handbook of Medicine for Final Year Students. By G. F. Walker, M.D., M.R.C.P. (Lond.), consulting physician, Peterborough Memorial Hospital. Fourth edition. 12° cloth, 308 pp. London: S. & S. W. Publications Ltd. 1948. 25s.

This manual, first published in 1931 and now in its fourth edition, has been thoroughly revised and brought up to date. It covers the whole field of medicine and naturally reflects the British point of view. The small volume is well published.

Occupational Therapy Source Book. Edited by Sidney Licht, M.D., with an introduction by C. Charles Burlingame, M.D., psychiatrist-in-chief, The Institute of Living. 4° cloth, 90 pp. Baltimore: Williams and Wilkins Company, 1948. \$1.00.

Dr. Licht has brought together in this volume ten extracts on occupational therapy in mental diseases from the works of pioneers in the field of psychiatry ranging from Pinel (1801) to Reid (1914). Other authors represented and the dates of their publications are Reil (1803), Hallaran (1810), Benjamin Rush (1812), Tuke (1816), Esquirol (1838), Leuret

been recommended by the experts and are going into effect with the current volume a weekly index of our loyal advertisers, and an insignia, adopted after much deliberation, that is truly representative of the *Journal* itself and its distinguished, if somewhat provincial, ancestry. The final form of the seal now appearing on the cover was suggested and drafted by Dr. Harold Bowditch.

In hoc signo vinces or — something like that!

It would be absolute madness, indeed, to trust a confirmed cholera patient to a few drops of camphor spirits, or three grains of *sulphur* and charcoal.

He who depends

Upon such favors, swims with fins of lead,
And hews down oaks with rushes

Boston M & S J, July 4, 1849

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

WOOD-TICK STUDY IN 1949

Some further progress will be made on the wood-tick study during the present season, although it was not possible to get into the field when the ticks first emerged, because funds had not been made available.

The funds that will be used this year represent the small balance left over from the study authorized in 1948. They will be used largely in determination of the results of spraying by other agencies in areas where ticks are prevalent, since it will not be possible for the Department to do any spraying studies this year with the small amount of funds. It is expected that the Legislature will make additional funds available for studies to be carried out in 1950. If so, experiments on the control can be begun as soon as the ticks begin to emerge from hibernation in order to study how long sprays will be effective in keeping down the tick population.

The Department is very much interested in receiving information from any persons or organizations that attempt to control ticks by sprays during the present season. It wishes to have on hand the best information regarding the possible methods of control so that those who expend their funds for the purpose will derive the greatest benefit from their operations.

The Department is particularly anxious to obtain information and receive specimens of ticks found inland more than fifteen miles from the seacoast. Up to the present time most of the tick-infested areas have been located near the coast.

UNUSUAL SEROLOGIC TESTS

Some of the unusual serologic tests formerly performed at the National Institutes of Health are now being done entirely at the Communicable Disease Center in Georgia. These are tests for amebiasis, trichinosis, echinococcosis and leptospirosis. Specimens for these tests should hereafter be sent to the Immunology-Serology Laboratory, Communicable Disease Center, United States Public Health Service, Chamblee, Georgia.

Blood specimens for serologic tests for trypanosomiasis, schistosomiasis, filariasis, leishmaniasis and toxoplasmosis should still be sent to the Laboratory of Tropical Diseases, National Institutes of Health, Bethesda 14, Maryland.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1949

DISEASE	RESUME		
	MAY 1949	MAY 1948	SEVEN YEAR MEDIAN
Chancroid	4	2	2*
Chicken pox	2233	1612	1763
Diphtheria	42	14	16
Dog bite	1472	1237	1269
Dysentery bacillary	4	8	8
German measles	1243	132	381
Gonorrhea	254	218	340
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	2	2*
Malaria	2	1	12
Measles	2327	5743	3320
Meningitis meningococcal	4	5	16
Meningitis Pfeiffer bacillus	3	5	2
Meningitis pneumococcal	0	2	4
Meningitis staphylococcal	1	0	0
Meningitis streptococcal	0	1	1
Meningitis undetermined	3	4	4
Mumps	1057	2403	1459
Poliomyelitis	10	0	1
Salmonellosis	2	6	6
Scarlet fever	649	908	1120
Syphilis	216	182	539
Tuberculosis pulmonary	243	207	279
Tuberculosis other forms	23	11	18
Typhoid fever	6	5	2
Undulant fever	4	4	4
Whooping cough	389	132	537

* Five-year median

COMMENT

Diseases above the seven-year median were chicken pox, diphtheria, German measles, poliomyelitis and typhoid fever. Diseases below the seven-year median were measles, meningitis, mumps, scarlet fever and whooping cough.

Diphtheria continued to be unusually prevalent, remaining at the level of fifteen years ago for this season. The incidence of poliomyelitis was the highest for May since 1935, but 6 of the cases were widely scattered along the seacoast. German measles continued its upward trend, suggesting that the next season may bring an epidemic.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Beverly, 1, Boston, 2, Cambridge, 6, Canton, 1, Malden, 2, New Bedford, 1, Newton, 1, Shirley, 1, Somerville, 1, Winthrop, 1, total, 4. Dysentery, bacillary, was reported from Pittsfield, 1, Waltham, 2, Winthrop, 1, total, 4.

Encephalitis, infectious, was reported from Lowell, 1, Rehoboth, 1, Sterling, 1, total, 3.

Infectious hepatitis was reported from Lowell, 1, Norwood, 1, Wrentham, 2, total, 4.

Malaria was reported from Lowell, 1, Swampscott, 1, total, 2.

Meningitis, meningococcal, was reported from Agawam, 1, Boston, 1, Lawrence, 1, Needham, 1, total, 4.

Meningitis, Pfeiffer bacillus, was reported from Brockton, 1, total, 1.

Meningitis, staphylococcus, was reported from Wrentham, 1, total, 1.

Meningitis, undetermined, was reported from Arlington, 1, Brockton, 1, Taunton, 1, total, 3
 Poliomelitis was reported from Arlington 1, Braintree 1, Brookline, 1, Cambridge, 1, Milton, 4, Newbury 1, Wareham, 1, total, 10
 Salmonellosis was reported from Leominster, 1, Peabody 1, total, 2
 Septic sore throat was reported from Boston, 2, Lynn, 1, Worcester, 1, total, 4
 Typhoid fever was reported from East Longmeadow 1, Everett, 2, Leominster, 1, Peabody, 1, Somerville 1, total 6
 Typhus fever was reported from Boston, 1, total 1
 Undulant fever was reported from Boxboro, 1, Maynard 1, Natick, 1, Pepperell, 1, total, 4

MISCELLANY

BOSTON UNIVERSITY ORGANIZES DEPARTMENT OF LEGAL MEDICINE

Dr Walter Jetter, pathologist for the Massachusetts Department of Mental Health and assistant professor of legal medicine at Harvard Medical School, has been selected by the trustees of Boston University to head a new department of legal medicine at Boston University School of Medicine. He will assume his new duties on July 1.

Dr Jetter was born in Buffalo, New York, on September 4, 1905. He received his M.D. degree from the University of Buffalo School of Medicine in 1931 and his M.S. in medicine in 1938 from the same school.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Ärztliche Rheokardiographie. By Wolfgang Holzer and Kurt Polzer. 8°, paper, 144 pp., with 88 illustrations and 3 tables. Vienna: Verlag Wilhelm Maudrich, 1948. \$3.00. *Bücher der physikalischen Medizin*. Volume III.

This monograph is comprehensive in scope, discussing the method in general, animal experimentation and the normal rheocardiogram in man, and in diseased conditions of the heart. The pertinent literature is noted throughout the text, which is concluded with an extensive bibliography of sources mentioned in the text and dating to 1947. There is a good index. The material is well arranged. The monograph is well published in a typical German style. It should be available to all persons interested in cardiology.

Bacterial and Mycotic Infections of Man. Edited by René J. Dubos, Ph.D., The Rockefeller Institute for Medical Research. 4°, cloth, 785 pp., with 101 illustrations, including 3 plates in color. Philadelphia: J. B. Lippincott Company, 1948. \$5.00.

This comprehensive treatise on medical bacteriology is a companion volume to *Viral and Rickettsial Infections of Man*, edited by Dr. Thomas M. Rivers and published by Lippincott in 1948. Thirty-four authors collaborated in the production of the volume. The beginning chapters deal with general principles and are followed by discussions of the various bacteria, spirochetes and mycoses. The concluding chapters are devoted to sterilization, chemotherapy, epidemiology and the cultivation and identification of pathogenic bacteria. The material is well arranged. There are lists of selected references appended to the various chapters. The text is concluded with comprehensive indexes of authors and subjects. The book is well published but since it weighs nearly 5 pounds a lighter paper, if possible, should have been used. This should be considered an essential reference book for all medical libraries and should be available to all persons interested in bacteriology and bacterial diseases.

The Digestive Tract in Roentgenology. By Jacob Buckstein, M.D., assistant professor of clinical medicine, Cornell University Medical College, visiting roentgenologist (alimentary tract division), Bellevue Hospital, New York City, attending gastroenterologist, Beth David Hospital, New York City and consultant in gastroenterology, Central Islip State Hospital, New York. 4°, cloth, 889 pp., with 1030 illustrations. Philadelphia: J. B. Lippincott Company, 1948. \$16.00.

This treatise is based on the author's experience of twenty years at Bellevue Hospital, where an enormous amount of material was available, and also on his private practice as a gastroenterologist. The material is well arranged and lists of references are appended to the various chapters. The pertinent literature is reviewed in each special chapter. Indexes of authors and of subjects are referred to throughout the text. The volume is well published and is recommended as a standard reference work for all medical libraries and to all roentgenologists.

Selected Diseases of Man. By C. E. van Rooven, M.D., D.Sc., F.R.C.P. (Lond.), research member and professor of virus infections, Connaught Medical Research Laboratories and School of Hygiene, University of Toronto and A. J. Rhodes, M.D., F.R.C.P. (Edin.), research associate and professor of virus infections, Connaught Medical Research Laboratories and School of Hygiene, University of Toronto and consultant in virus infections, Hospital for Sick Children, Toronto. 8°, cloth, 1202 pp., with 43 illustrations. New York: Thomas Nelson and Sons, 1948. \$22.50.

This edition of a standard reference work first published in 1940 has been thoroughly revised in the light of the knowledge of the subject gained during the past ten years. The literature has been surveyed through 1947 with the addition of some papers published during the early months of 1948. Selected references are appended to each chapter. The latest information on two diseases prevalent in the United States—influenza and poliomyelitis—is given at length. All the diseases now attributed to viruses are discussed in detail. The type and printing are good, but the use of a coated paper making the volume weigh more than 5 pounds, is not justified by the few illustrations. The book should be in all medical libraries and should be available to all general practitioners.

The Commonsense Psychiatry of Dr. Adolf Meyer. Fifty-two selected papers edited, with biographical narrative, by Alfred Lief. 8°, cloth, 677 pp. New York: McGraw-Hill Book Company, Inc., 1948. \$6.50.

This volume constitutes a collection of fifty-two papers of Dr. Meyer brought together from scattered sources and reprinted in one volume for convenience for reference purposes. A short biographic sketch precedes the papers. A glossary and an index conclude the volume. The publishing is excellent. The book is recommended for all medical libraries and should be available to all psychiatrists.

Handbook of Medicine for Final Year Students. By G. F. Walker, M.D., M.R.C.P. (Lond.), consulting physician, Peterborough Memorial Hospital. Fourth edition. 12°, cloth, 308 pp. London: S. K. & S. P. Publications Ltd., 1948. 25s.

This manual, first published in 1931 and now in its fourth edition, has been thoroughly revised and brought up to date. It covers the whole field of medicine and naturally reflects the British point of view. The small volume is well published.

Occupational Therapy Source Book. Edited by Sidney Licht, M.D., with an introduction by C. Charles Burlingame, M.D., psychiatrist-in-chief, The Institute of Living. 4°, cloth, 90 pp. Baltimore: Williams and Wilkins Company, 1948. \$1.00.

Dr. Licht has brought together in this volume ten extracts on occupational therapy in mental diseases from the works of pioneers in the field of psychiatry ranging from Pinel (1801) to Reid (1914). Other authors represented and the dates of their publications are Reil (1803), Hallaran (1810), Benjamin Rush (1812), Tuke (1816), Esquirol (1838), Leuret

(1840), Voisin (1843) and Kirkbride (1880). The paper of Dr. Reid on "ergotherapy in the treatment of mental disorders" was originally published in the *Boston Medical and Surgical Journal*. The extracts are preceded by a long outline of the early history of occupational therapy, dating from the Hippocratic era to 1915, written by Dr. Licht. The volume is well published, and the price is very reasonable. The book should be in all medical libraries, in all medical-history collections and in the collections of persons interested in the subject.

Pediatrics and the Emotional Needs of the Child As discussed by pediatricians and psychiatrists at Hershey, Pennsylvania, March 6-8, 1947. Edited by Helen I. Witmer. 8°, paper, 180 pp., with 17 illustrations. New York: Commonwealth Fund, 1948. \$1.50.

This conference was participated in by 48 physicians and social workers. The various aspects of the subject were discussed in detail in five meetings. An appendix comprises reports from the psychiatric services or child-guidance clinics of ten prominent hospitals. The volume is well published and should be in all collections on pediatrics, psychiatry and applied psychology. It should prove useful to social workers.

An Introduction to Surgery. By Rutherford Morison, M.D., F.R.C.S. Edin., F.R.C.S. Eng., M.A., D.C.I., LL.D., and Charles F. M. Saint, C.B.E., M.D., M.S., F.R.C.S., F.R.A.C.S. Fourth edition. 8°, cloth, 330 pp., with 304 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$10.00.

This small manual, designed for the student of surgery, was revised and brought up to date by Dr. Saint after the death of Dr. Morison. It constitutes on the whole a short work on surgical pathology. The material is well organized, and the text well illustrated. The printing was done in Great Britain, and the publishing is excellent.

A M.A. Interns' Manual. 12°, cloth, 201 pp. Philadelphia: W. B. Saunders Company, 1948. \$2.25.

This small volume was originally published in 1938 under the present title. It was the successor to *Hospital Practice for Internes*, first published in 1932. The text has been prepared by the various councils of the Association, and is divided into seven principal sections, as follows: internships and residencies — general information, clinical and laboratory data, including common emergencies, drug administration, materia medica — useful drugs, acute poisoning (diagnosis and treatment), diet and nutrition and physical medicine. Parts two to seven supply the intern with the essential facts needed in his daily practice. The eighth part, the "Lawful Scope of Intern Practice," is an important contribution on the legal status of interns in the various states. The last part is a short description of the American Medical Association and its subdivisions. There is an index. The publishing is excellent. The book should prove exceedingly useful to all interns.

NOTICES

MASSACHUSETTS TRUDEAU SOCIETY

At a meeting of the Massachusetts Trudeau Society on June 9, the following officers were elected: president, Henry D. Chidwick, of Waltham; vice-president, Francis P. Dawson, of Waltham; and secretary-treasurer, Edward J. Welch, of Brookline.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 6-10 American Congress of Physical Medicine. Page xii issue of March 24.

SEPTEMBER 8 Care of the Terminal Stage of Cancer. Dr. John W. Spellman. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 28-30 Mississippi Valley Medical Society. Page 1000 issue of December 30.

OCTOBER 11-15 American Society of Clinical Pathologists. Drake Hotel, Chicago.

NOVEMBER 2 New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 3-5 American Association of Blood Banks. Page xi issue of June 16.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 14

FRIDAY, JULY 15

*9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*1:30 p.m. Tumor Clinic. Out Patient Department. Mt. Auburn Hospital, Cambridge.

MONDAY, JULY 18

*11:30 a.m.-12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleveland Floyd in charge.

*12:15-1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, JULY 19

*12:15-1:15 p.m. Clinicoradiogenetological Conference. Peter Bent Brigham Hospital.

*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

WEDNESDAY, JULY 20

*12:00 p.m.-1:00 p.m. Clinical Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

*Open to the medical profession.



Use herbs of conservative brewing,

Says Doc Wise, to avoid future ruing

For drugs that are sound

In the Journal are found —

Not the pharmacopeia of Ewing

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MEDICAL SCIENCE UNDER DICTATORSHIP

LEO ALEXANDER M.D.*

BOSTON

SCIENCE under dictatorship becomes subordinated to the guiding philosophy of the dictatorship. Irrespective of other ideologic trappings, the guiding philosophic principle of recent dictatorships, including that of the Nazis, has been Hegelian in that what has been considered "rational utility" and corresponding doctrine and planning has replaced moral, ethical and religious values. Nazi propaganda was highly effective in perverting public opinion and public conscience, in a remarkably short time. In the medical profession this expressed itself in a rapid decline in standards of professional ethics. Medical science in Nazi Germany collaborated with this Hegelian trend particularly in the following enterprises: the mass extermination of the chronically sick in the interest of saving "useless" expenses to the community as a whole, the mass extermination of those considered socially disturbing or racially and ideologically unwanted, the individual, inconspicuous extermination of those considered disloyal within the ruling group, and the ruthless use of "human experimental material" for medicomilitary research.

This paper discusses the origins of these activities, as well as their consequences upon the body social, and the motivation of those participating in them.

Preparatory Propaganda

Even before the Nazis took open charge in Germany, a propaganda barrage was directed against the traditional compassionate nineteenth-century attitudes toward the chronically ill, and for the adoption of a utilitarian, Hegelian point of view. Sterilization and euthanasia of persons with chronic mental illnesses was discussed at a meeting of Bavarian psychiatrists in 1931.¹ By 1936 extermination of the physically or socially unfit was so openly accepted that its practice was mentioned incidentally in an article published in an official German medical journal.²

Lay opinion was not neglected in this campaign. Adults were propagandized by motion pictures,

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one of which, entitled "I Accuse," deals entirely with euthanasia. This film depicts the life history of a woman suffering from multiple sclerosis, in it her husband, a doctor, finally kills her to the accompaniment of soft piano music rendered by a sympathetic colleague in an adjoining room. Acceptance of this ideology was implanted even in the children. A widely used high-school mathematics text, "Mathematics in the Service of National Political Education,"³ includes problems stated in distorted terms of the cost of caring for and rehabilitating the chronically sick and crippled. One of the problems asked, for instance, how many new housing units could be built and how many marriage-allowance loans could be given to newly wedded couples for the amount of money it cost the state to care for "the crippled, the criminal and the insane."

Euthanasia

The first direct order for euthanasia was issued by Hitler on September 1, 1939, and an organization was set up to execute the program. Dr. Karl Brandt headed the medical section, and Phillip Bouhler the administrative section. All state institutions were required to report on patients who had been ill five years or more and who were unable to work, by filling out questionnaires giving name, race, marital status, nationality, next of kin, whether regularly visited and by whom, who bore financial responsibility and so forth. The decision regarding which patients should be killed was made entirely on the basis of this brief information by expert consultants, most of whom were professors of psychiatry in the key universities. These consultants never saw the patients themselves. The thoroughness of their scrutiny can be appraised by the work of one expert, who between November 14 and December 1, 1940, evaluated 2109 questionnaires.

These questionnaires were collected by a "Realm's Work Committee of Institutions for Cure and Care."⁴ A parallel organization devoted exclusively to the killing of children was known by the similarly euphemistic name of "Realm's Committee for Scientific Approach to Severe Illness Due to Heredity and Constitution." The "Charitable

Transport Company for the Sick" transported patients to the killing centers, and the "Charitable Foundation for Institutional Care" was in charge of collecting the cost of the killings from the relatives, without, however, informing them what the charges were for, in the death certificates the cause of death was falsified.

What these activities meant to the population at large was well expressed by a few hardy souls who dared to protest. A member of the court of appeals at Frankfurt-am-Main wrote in December, 1939

There is constant discussion of the question of the destruction of socially unfit life—in the places where there are mental institutions, in neighboring towns, sometimes over a large area, throughout the Rhineland, for example. The people have come to recognize the vehicles in which the patients are taken from their original institution to the intermediate institution and from there to the liquidation institution. I am told that when they see these buses even the children call out "They're taking some more people to be gassed." From Limburg it is reported that every day from one to three buses with shades drawn pass through on the way from Weilmünster to Hadamar, delivering inmates to the liquidation institution there. According to the stories the arrivals are immediately stripped to the skin, dressed in paper shirts, and forthwith taken to a gas chamber, where they are liquidated with hydrocyanic acid gas and an added anesthetic. The bodies are reported to be moved to a combustion chamber by means of a conveyor belt, six bodies to a furnace. The resulting ashes are then distributed into six urns which are shipped to the families. The heavy smoke from the crematory building is said to be visible over Hadamar every day. There is talk, furthermore, that in some cases heads and other portions of the body are removed for anatomical examination. The people working at this liquidation job in the institutions are said to be assigned from other areas and are shunned completely by the populace. This personnel is described as frequenting the bars at night and drinking heavily. Quite apart from these overt incidents that exercise the imagination of the people, they are disquieted by the question of whether old folk who have worked hard all their lives and may merely have come into their dotage are also being liquidated. There is talk that the homes for the aged are to be cleaned out too. The people are said to be waiting for legislative regulation providing some orderly method that will insure especially that the aged feeble-minded are not included in the program.

Here one sees what "euthanasia" means in actual practice. According to the records, 275,000 people were put to death in these killing centers. Ghastly as this seems, it should be realized that this program was merely the entering wedge for exterminations of far greater scope in the political program for genocide of conquered nations and the racially unwanted. The methods used and personnel trained in the killing centers for the chronically sick became the nucleus of the much larger centers in the East, where the plan was to kill all Jews and Poles and to cut down the Russian population by 30,000,000.

The original program developed by Nazi hot-heads included also the genocide of the English, with the provision that the English males were to be used as laborers in the vacated territories in the East, there to be worked to death, whereas the English females were to be brought into Germany

to improve the qualities of the German race (This was indeed a peculiar admission on the part of the German eugenicists).

In Germany the exterminations included the mentally defective, psychotics (particularly schizophrenics), epileptics and patients suffering from infirmities of old age and from various organic neurologic disorders such as infantile paralysis, Parkinsonism, multiple sclerosis and brain tumors. The technical arrangements, methods and training of the killer personnel were under the direction of a committee of physicians and other experts headed by Dr. Karl Brandt. The mass killings were first carried out with carbon monoxide gas, but later cyanide gas ("cyclon B") was found to be more effective. The idea of camouflaging the gas chambers as shower baths was developed by Brack, who testified before Judge Sebring that the patients walked in calmly, deposited their towels and stood with their little pieces of soap under the shower outlets, waiting for the water to start running. This statement was ample rebuttal of his claim that only the most severely regressed patients among the mentally sick and only the moribund ones among the physically sick were exterminated. In truth, all those unable to work and considered nonrehabilitable were killed.

All but their squeal was utilized. However, the program grew so big that even scientists who hoped to benefit from the treasure of material supplied by this totalitarian method were disappointed. A neuropathologist, Dr. Hallervorden, who had obtained 500 brains from the killing centers for the insane, gave me a vivid first-hand account.⁵ The Charitable Transport Company for the Sick brought the brains in batches of 150 to 250 at a time. Hallervorden stated:

There was wonderful material among those brains, beautiful mental defectives, malformations and early infantile diseases. I accepted those brains of course. Where they came from and how they came to me was really none of my business.

In addition to the material he wanted, all kinds of other cases were mixed in, such as patients suffering from various types of Parkinsonism, simple depressions, involutional depressions and brain tumors, and all kinds of other illnesses, including psychopathy that had been difficult to handle.

These were selected from the various wards of the institutions according to an excessively simple and quick method. Most institutions did not have enough physicians, and what physicians there were were either too busy or did not care, and they delegated the selection to the nurses and attendants. Whoever looked sick or was otherwise a problem was put on a list and was transported to the killing center. The worst thing about this business was that it produced a certain brutalization of the nursing personnel. They got to simply picking out those whom they did not like, and the doctors had so many patients that they did not even know them, and put their names on the list.

Of the patients thus killed, only the brains were sent to Dr. Hallervorden, they were killed in such

large numbers that autopsies of the bodies were not feasible. That in Dr Hallervorden's opinion, greatly reduced the scientific value of the material. The brains, however, were always well fixed and suspended in formalin exactly according to his instructions. He thinks that the cause of psychiatry was permanently injured by these activities and that psychiatrists have lost the respect of the German people forever. Dr Hallervorden concluded: "Still, there were interesting cases in this material."

In general only previously hospitalized patients were exterminated for reasons of illness. An exception is a program carried out in a northwestern district of Poland, the "Warthegau" where a health survey of the entire population was made by an "SS X-Ray Battalion" headed by Professor Hohlfelder, radiologist of the University of Frankfurt-am-Main. Persons found to be infected with tuberculosis were carted off to special extermination centers.

It is rather significant that the German people were considered by their Nazi leaders more ready to accept the exterminations of the sick than those for political reasons. It was for that reason that the first exterminations of the latter group were carried out under the guise of sickness. So-called "psychiatric experts" were dispatched to survey the inmates of camps with the specific order to pick out members of racial minorities and political offenders from occupied territories and to dispatch them to killing centers with specially made diagnoses such as that of "inveterate German hater" applied to a number of prisoners who had been active in the Czech underground.

Certain classes of patients with mental diseases who were capable of performing labor, particularly members of the armed forces suffering from psychopathy or neurosis, were sent to concentration camps to be worked to death, or to be reassigned to punishment battalions and to be exterminated in the process of removal of mine fields.⁶

A large number of those marked for death for political or racial reasons were made available for "medical" experiments involving the use of involuntary human subjects. From 1942 on, such experiments carried out in concentration camps were openly presented at medical meetings. This program included "terminal human experiments," a term introduced by Dr Rascher to denote an experiment so designed that its successful conclusion depended upon the test person's being put to death.

The Science of Annihilation

A large part of this research was devoted to the science of destroying and preventing life, for which I have proposed the term "ktenology," the science of killing.⁷⁻⁹ In the course of this ktenologic research, methods of mass killing and mass sterilization were investigated and developed for use against non-

German peoples or Germans who were considered useless.

Sterilization methods were widely investigated, but proved impractical in experiments conducted in concentration camps. A rapid method developed for sterilization of females, which could be accomplished in the course of a regular health examination, was the intra-uterine injection of various chemicals. Numerous mixtures were tried, some with iodopine and others containing barium, another was most likely silver nitrate with iodized oil, because the result could be ascertained by x-ray examination. The injections were extremely painful and a number of women died in the course of the experiments. Professor Karl Clauberg reported that he had developed a method at the Auschwitz concentration camp by which he could sterilize 1000 women in one day.

Another method of sterilization, or rather castration, was proposed by Viktor Brack especially for conquered populations. His idea was that x-ray machinery could be built into desks at which the people would have to sit, ostensibly to fill out a questionnaire requiring five minutes, they would be sterilized without being aware of it. This method failed because experiments carried out on 100 male prisoners brought out the fact that severe x-ray burns were produced on all subjects. In the course of this research, which was carried out by Dr Horst Schuman, the testicles of the victims were removed for histologic examination two weeks later. I myself examined 4 castrated survivors of this ghastly experiment. Three had extensive necrosis of the skin near the genitalia, and the other an extensive necrosis of the urethra. Other experiments in sterilization used an extract of the plant *Caladium seguinum*, which had been shown in animal studies by Madaus and his co-workers^{10, 11} to cause selective necrosis of the germinal cells of the testicles as well as the ovary.

The development of methods for rapid and inconspicuous individual execution was the objective of another large part of the ktenologic research. These methods were to be applied to members of the ruling group, including the SS itself, who were suspected of disloyalty. This, of course is an essential requirement in a dictatorship, in which "cut-throat competition" becomes a grim reality and any hint of faintheartedness or lack of enthusiasm for the methods of totalitarian rule is considered a threat to the entire group.

Poisons were the subject of many of these experiments. A research team at the Buchenwald concentration camp, consisting of Drs Joachim Mrugowsky, Erwin Ding-Schuler and Waldemar Hoven, developed the most widely used means of individual execution under the guise of medical treatment — namely, the intravenous injection of phenol or gasoline. Several alkaloids were also investigated, among them aconitine, which was used

by Dr Hoven to kill several imprisoned former fellow SS men who were potential witnesses against the camp commander, Koch, then under investigation by the SS. At the Dachau concentration camp Dr Rascher developed the standard cyanide capsules, which could be easily bitten through, either deliberately or accidentally, if mixed with certain foods, and which, ironically enough, later became the means with which Himmler and Goering killed themselves. In connection with these poison experiments there is an interesting incident of characteristic sociologic significance. When Dr Hoven was under trial by the SS the investigating SS judge, Dr Morgen, proved Hoven's guilt by feeding the poison found in Dr Hoven's possession to a number of Russian prisoners of war, these men died with the same symptoms as the SS men murdered by Dr Hoven. This worthy judge was rather proud of this efficient method of proving Dr Hoven's guilt and appeared entirely unaware of the fact that in the process he had committed murder himself.

Poisons, however, proved too obvious or detectable to be used for the elimination of high-ranking Nazi party personnel who had come into disfavor, or of prominent prisoners whose deaths should appear to stem from natural causes. Phenol or gasoline, for instance, left a telltale odor with the corpse. For this reason a number of more subtle methods were devised. One of these was artificial production of septicemia. An intramuscular injection of 1 cc of pus, containing numerous chains of streptococci, was the first step. The site of injection was usually the inside of the thigh, close to the adductor canal. When an abscess formed it was tapped, and 3 cc of the creamy pus removed was injected intravenously into the patient's opposite arm. If the patient then died from septicemia, the autopsy proved that death was caused by the same organism that had caused the abscess. These experiments were carried out in many concentration camps. At the Dachau camp the subjects were almost exclusively Polish Catholic priests. However, since this method did not always cause death, sometimes resulting merely in a local abscess, it was considered inefficient, and research was continued with other means but along the same lines.

The final triumph of the part of ktenology research aimed at finding a method of inconspicuous execution that would produce autopsy findings indicative of death from natural causes was the development of repeated intravenous injections of suspensions of live tubercle bacilli, which brought on acute military tuberculosis within a few weeks. This method was produced by Professor Dr Heissmeyer, who was one of Dr Gebhardt's associates at the SS hospital of Hohenlychen. As a means of further camouflage, so that the SS at large would not suspect the purpose of these experiments, the preliminary tests for the efficacy of this method

were performed exclusively on children imprisoned in the Neuengamme concentration camp.

For use in "medical" executions of prisoners and of members of the SS and other branches of the German armed forces the use of simple lethal injections, particularly phenol injections, remained the instrument of choice. Whatever methods he used, the physician gradually became the unofficial executioner, for the sake of convenience, informality and relative secrecy. Even on German submarines it was the physician's duty to execute the trouble-makers among the crew by lethal injections.

Medical science has for some time been an instrument of military power in that it preserved the health and fighting efficiency of troops. This essentially defensive purpose is not inconsistent with the ethical principles of medicine. In World War I the German empire had enlisted medical science as an instrument of aggressive military power by putting it to use in the development of gas warfare. It was left to the Nazi dictatorship to make medical science into an instrument of political power—a formidable, essential tool in the complete and effective manipulation of totalitarian control. This should be a warning to all civilized nations, and particularly to individuals who are blinded by the "efficiency" of a totalitarian rule, under whatever name.

This entire body of research as reported so far served the master crime to which the Nazi dictatorship was committed—namely, the genocide of non-German peoples and the elimination by killing, in groups or singly, of Germans who were considered useless or disloyal. In effecting the two parts of this program, Himmler demanded and received the co-operation of physicians and of German medical science. The result was a significant advance in the science of killing, or ktenology.

Medicomilitary Research

Another chapter in Nazi scientific research was that aimed to aid the military forces. Many of these ideas originated with Himmler, who fancied himself a scientist.

When Himmler learned that the cause of death of most SS men on the battlefield was hemorrhage, he instructed Dr Sigmund Rascher to search for a blood coagulant that might be given before the men went into action. Rascher tested this coagulant when it was developed by clocking the number of drops emanating from freshly cut amputation stumps of living and conscious prisoners at the crematorium of Dachau concentration camp and by shooting Russian prisoners of war through the spleen.

Live dissections were a feature of another experimental study designed to show the effects of explosive decompression¹²⁻¹⁴. A mobile decompression chamber was used. It was found that when subjects were made to descend from altitudes of 40,000 to 60,000 feet without oxygen, severe symptoms

of cerebral dysfunction occurred — at first convulsions, then unconsciousness in which the body was hanging limp and later, after waking, temporary blindness, paralysis or severe confusional twilight states. Rascher, who wanted to find out whether these symptoms were due to anoxic changes or to other causes, did what appeared to him the most simple thing: he placed the subjects of the experiment under water and dissected them while the heart was still beating, demonstrating air embolism in the blood vessels of the heart, liver, chest wall and brain.

Another part of Dr Rascher's research, carried out in collaboration with Holzlochner and Finke, concerned shock from exposure to cold.¹⁵ It was known that military personnel generally did not survive immersion in the North Sea for more than sixty to a hundred minutes. Rascher therefore attempted to duplicate these conditions at Dachau concentration camp and used about 300 prisoners in experiments on shock from exposure to cold, of these 80 or 90 were killed. (The figures do not include persons killed during mass experiments on exposure to cold outdoors.) In one report on this work Rascher asked permission to shift these experiments from Dachau to Auschwitz, a larger camp where they might cause less disturbance because the subjects shrieked from pain when their extremities froze white. The results like so many of those obtained in the Nazi research program, are not dependable. In his report Rascher stated that it took from fifty-three to a hundred minutes to kill a human being by immersion in ice water — a time closely in agreement with the known survival period in the North Sea. Inspection of his own experimental records and statements made to me by his close associates showed that it actually took from eighty minutes to five or six hours to kill an undressed person in such a manner, whereas a man in full aviator's dress took six or seven hours to kill. Obviously, Rascher dressed up his findings to forestall criticism, although any scientific man should have known that during actual exposure many other factors, including greater convection of heat due to the motion of water, would affect the time of survival.

Another series of experiments gave results that might have been an important medical contribution if an important lead had not been ignored. The efficacy of various vaccines and drugs against typhus was tested at the Buchenwald and Natzweiler concentration camps. Prevaccinated persons and non-vaccinated controls were injected with live typhus rickettsias, and the death rates of the two series compared. After a certain number of passages, the Matelska strain of typhus rickettsia proved to become avirulent for man. Instead of seizing upon this as a possibility to develop a live vaccine, the experimenters including the chief consultant, Professor Gerhard Rose, who should have known better,

were merely annoyed at the fact that the controls did not die either, discarded this strain and continued testing their relatively ineffective dead vaccines against a new virulent strain. This incident shows that the basic unconscious motivation and attitude has a great influence in determining the scientist's awareness of the phenomena that pass through his vision.

Sometimes human subjects were used for tests that were totally unnecessary, or whose results could have been predicted by simple chemical experiments. For example, 90 gypsies were given unaltered sea water and sea water whose taste was camouflaged as their sole source of fluid, apparently to test the well known fact that such hypertonic saline solutions given as the only source of supply of fluid will cause severe physical disturbance or death within six to twelve days. These persons were subjected to the tortures of the damned, with death resulting in at least 2 cases.

Heteroplastic transplantation experiments were carried out by Professor Dr Karl Gebhardt at Himmler's suggestion. Whole limbs — shoulder, arm or leg — were amputated from live prisoners at Ravensbrueck concentration camp, wrapped in sterile moist dressings and sent by automobile to the SS hospital at Hohenlychen where Professor Gebhardt busied himself with a futile attempt at heteroplastic transplantation. In the meantime the prisoners deprived of a limb were usually killed by lethal injection.

One would not be dealing with German science if one did not run into manifestations of the collector's spirit. By February 1942 it was assumed in German scientific circles that the Jewish race was about to be completely exterminated, and alarm was expressed over the fact that only very few specimens of skulls and skeletons of Jews were at the disposal of science. It was therefore proposed that a collection of 150 body casts and skeletons of Jews be preserved for perusal by future students of anthropology. Dr August Hirt, professor of anatomy at the University of Strassburg, declared himself interested in establishing such a collection at his anatomic institute. He suggested that captured Jewish officers of the Russian armed forces be included, as well as females from Auschwitz concentration camp, that they be brought alive to Natzweiler concentration camp near Strassburg, and that after "their subsequently induced death — care should be taken that the heads not be damaged [sic]" the bodies be turned over to him at the anatomic institute of the University of Strassburg. This was done. The entire collection of bodies and the correspondence pertaining to it fell into the hands of the United States Army.

One of the most revolting experiments was the testing of sulfonamides against gas gangrene by Professor Gebhardt and his collaborators for which young women captured from the Polish Resistance

Movement served as subjects. Necrosis was produced in a muscle of the leg by ligation and the wound was infected with various types of gas-gangrene bacilli, frequently, dirt, pieces of wood and glass splinters were added to the wound. Some of these victims died and others sustained severe mutilating deformities of the leg.

Motivation

An important feature of the experiments performed in concentration camps is the fact that they not only represented a ruthless and callous pursuit of legitimate scientific goals but also were motivated by rather sinister practical ulterior political and personal purposes, arising out of the requirements and problems of the administration of totalitarian rule.

Why did men like Professor Gebhardt lend themselves to such experiments? The reasons are fairly simple and practical, no surprise to anyone familiar with the evidence of fear, hostility, suspicion, rivalry and intrigue, the fratricidal struggle euphemistically termed the "self-selection of leaders," that went on within the ranks of the ruling Nazi party and the SS. The answer was fairly simple and logical. Dr. Gebhardt performed these experiments to clear himself of the suspicion that he had been contributing to the death of SS General Reinhard ("The Hangman") Heydrich, either negligently or deliberately, by failing to treat his wound infection with sulfonamides. After Heydrich died from gas gangrene, Himmler himself told Dr. Gebhardt that the only way in which he could prove that Heydrich's death was "fate determined" was by carrying out a "large-scale experiment" in prisoners, which would prove or disprove that people died from gas gangrene irrespective of whether they were treated with sulfonamides or not.

Dr. Sigmund Rascher did not become the notorious vivisectionist of Dachau concentration camp and the willing tool of Himmler's research interests until he had been forbidden to use the facilities of the Pathological Institute of the University of Munich because he was suspected of having Communist sympathies. Then he was ready to go all out and to do anything merely to regain acceptance by the Nazi party and the SS.

These cases illustrate a method consciously and methodically used in the SS, an age-old method used by criminal gangs everywhere—that of making suspects of disloyalty clear themselves by participation in a crime that would definitely and irrevocably tie them to the organization. In the SS this process of reinforcement of group cohesion was called "Blutkitt" (blood-cement), a term that Hitler himself is said to have obtained from a book on Genghis Khan in which this technic was emphasized.

The important lesson here is that this motivation, with which one is familiar in ordinary crimes, applies also to war crimes and to ideologically conditioned

crimes against humanity—namely, that fear and cowardice, especially fear of punishment or of ostracism by the group, are often more important motives than simple ferocity or aggressiveness.

The Early Change in Medical Attitudes

Whatever proportions these crimes finally assumed, it became evident to all who investigated them that they had started from small beginnings. The beginnings at first were merely a subtle shift in emphasis in the basic attitude of the physicians. It started with the acceptance of the attitude, basic in the euthanasia movement, that there is such a thing as life not worthy to be lived. This attitude in its early stages concerned itself merely with the severely and chronically sick. Gradually the sphere of those to be included in this category was enlarged to encompass the socially unproductive, the ideologically unwanted, the racially unwanted and finally all non-Germans. But it is important to realize that the infinitely small wedged-in lever from which this entire trend of mind received its impetus was the attitude toward the nonrehabitable sick.

It is, therefore, this subtle shift in emphasis of the physicians' attitude that one must thoroughly investigate. It is a recent significant trend in medicine, including psychiatry, to regard prevention as more important than cure. Observation and recognition of early signs and symptoms have become the basis for prevention of further advance of disease.⁸

In looking for these early signs one may well retrace the early steps of propaganda on the part of the Nazis in Germany as well as in the countries that they overran and in which they attempted to gain supporters by means of indoctrination, seduction and propaganda.

The Example of Successful Resistance by the Physicians of the Netherlands

There is no doubt that in Germany itself the first and most effective step of propaganda within the medical profession was the propaganda barrage against the useless, incurably sick described above. Similar, even more subtle efforts were made in some of the occupied countries. It is to the everlasting honor of the medical profession of Holland that they recognized the earliest and most subtle phases of this attempt and rejected it. When Seiss-Inquart, Reich Commissar for the Occupied Netherlands Territories, wanted to draw the Dutch physicians into the orbit of the activities of the German medical profession, he did not tell them "You must send your chronic patients to death factories" or "You must give lethal injections at Government request in your offices," but he couched his order in most careful and superficially acceptable terms. One of the paragraphs in the order of the Reich Commissar of the Netherlands Territories concerning the Netherlands doctors of

19 December 1941 reads as follows "It is the duty of the doctor, through advice and effort, conscientiously and to his best ability, to assist as helper the person entrusted to his care in the maintenance, improvement and re-establishment of his vitality, physical efficiency and health. The accomplishment of this duty is a public task."¹⁶ The physicians of Holland rejected this order unanimously because they saw what it actually meant — namely, the concentration of their efforts on mere rehabilitation of the sick for useful labor, and abolition of medical secrecy. Although on the surface the new order appeared not too grossly unacceptable, the Dutch physicians decided that it is the first, although slight, step away from principle that is the most important one. The Dutch physicians declared that they would not obey this order. When Seiss-Inquart threatened them with revocation of their licenses, they returned their licenses, removed their shingles and, while seeing their own patients secretly, no longer wrote death or birth certificates. Seiss-Inquart retraced his steps and tried to cajole them — still to no effect. Then he arrested 100 Dutch physicians and sent them to concentration camps. The medical profession remained adamant and quietly took care of their widows and orphans, but would not give in. Thus it came about that not a single euthanasia or non-therapeutic sterilization was recommended or participated in by any Dutch physician. They had the foresight to resist before the first step was taken, and they acted unanimously and won out in the end. It is obvious that if the medical profession of a small nation under the conqueror's heel could resist so effectively, the German medical profession could likewise have resisted had they not taken the fatal first step. It is the first seemingly innocent step away from principle that frequently decides a career of crime. Corrosion begins in microscopic proportions.

The Situation in the United States

The question that this fact prompts is whether there are any danger signs that American physicians have also been infected with Hegelian, cold-blooded, utilitarian philosophy and whether early traces of it can be detected in their medical thinking that may make them vulnerable to departures of the type that occurred in Germany. Basic attitudes must be examined dispassionately. The original concept of medicine and nursing was not based on any rational or feasible likelihood that they could actually cure and restore but rather on an essentially maternal or religious idea. The Good Samaritan had no thought of nor did he actually care whether he could restore working capacity. He was merely motivated by the compassion in alleviating suffering. Bernal¹⁷ states that prior to the advent of scientific medicine, the physician's main function was to give hope

to the patient and to relieve his relatives of responsibility. Gradually, in all civilized countries, medicine has moved away from this position, strangely enough in direct proportion to man's actual ability to perform feats that would have been plain miracles in days of old. However, with this increased efficiency based on scientific development went a subtle change in attitude. Physicians have become dangerously close to being mere technicians of rehabilitation. This essentially Hegelian rational attitude has led them to make certain distinctions in the handling of acute and chronic diseases. The patient with the latter carries an obvious stigma as the one less likely to be fully rehabilitable for social usefulness. In an increasingly utilitarian society these patients are being looked down upon with increasing definiteness as unwanted ballast. A certain amount of rather open contempt for the people who cannot be rehabilitated with present knowledge has developed. This is probably due to a good deal of unconscious hostility, because these people for whom there seem to be no effective remedies have become a threat to newly acquired delusions of omnipotence.

Hospitals like to limit themselves to the care of patients who can be fully rehabilitated, and the patient whose full rehabilitation is unlikely finds himself, at least in the best and most advanced centers of healing, as a second-class patient faced with a reluctance on the part of both the visiting and the house staff to suggest and apply therapeutic procedures that are not likely to bring about immediately striking results in terms of recovery. I wish to emphasize that this point of view did not arise primarily within the medical profession, which has always been outstanding in a highly competitive economic society for giving freely and unstintingly of its time and efforts, but was imposed by the shortage of funds available, both private and public. From the attitude of easing patients with chronic diseases away from the doors of the best types of treatment facilities available to the actual dispatching of such patients to killing centers is a long but nevertheless logical step. Resources for the so-called incurable patient have recently become practically unavailable.

There has never in history been a shortage of money for the development and manufacture of weapons of war, there is and should be none now. The disproportion of monetary support for war and that available for healing and care is an anachronism in an era that has been described as the "enlightened age of the common man" by some observers. The comparable cost of jet planes and hospital beds is too obvious for any excuse to be found for a shortage of the latter. I trust that these remarks will not be misunderstood. I believe that armament, including jet planes, are vital for the security of the republic, but adequate maintenance of stand-

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mous" and, most recently the National Multiple Sclerosis Society. All these societies, which are co-ordinated with special medical societies and which received inspiration and guidance from outstanding physicians, are having an extremely wholesome effect in introducing fresh motivating power into the ivory towers of academic medicine. It is indeed interesting and an assertion of democratic vitality that these societies are activated by and for people suffering from illnesses who, under certain dictatorships, would have been slated for euthanasia.

It is thus that these new societies have taken over one of the ancient functions of medicine — namely, to give hope to the patient and to relieve his relatives. These societies need the whole-hearted support of the medical profession. Unfortunately, this support is by no means yet unanimous. A distinguished physician, investigator and teacher at an outstanding university recently told me that he was opposed to these special societies and clinics because they had nothing to offer to the patient. It would be better to wait until someone made a discovery accidentally and then start clinics. It is my opinion, however, that one cannot wait for that. The stimulus supplied by these societies is necessary to give stimulus both to public demand and to academic medicine, which at times grows stale and unproductive even in its most outstanding centers, and whose existence did nothing to prevent the executioner from having logic on his side in Germany.

Another element of this free democratic society and enterprise that has been a stimulus to new developments is the pharmaceutical industry, which, with great vision, has invested considerable effort in the sponsorship of new research.

Dictatorships can be indeed defined as systems in which there is a prevalence of thinking in destructive rather than in ameliorative terms in dealing with social problems. The ease with which destruction of life is advocated for those considered either socially useless or socially disturbing instead of educational or ameliorative measures may be the first danger sign of loss of creative liberty in thinking, which is the hallmark of democratic society. All destructiveness ultimately leads to self-destruction, the fate of the SS and of Nazi Germany is an eloquent example. The destructive principle, once unleashed, is bound to engulf the whole personality and to occupy all its relationships. Destructive urges and destructive concepts arising therefrom cannot remain limited or focused upon one sub-

ject or several subjects alone, but must inevitably spread and be directed against one's entire surrounding world, including one's own group and ultimately the self. The ameliorative point of view maintained in relation to all others is the only real means of self-preservation.

A most important need in this country is for the development of active and alert hospital centers for the treatment of chronic illnesses. They must have active staffs similar to those of the hospitals for acute illnesses, and these hospitals must be fundamentally different from the custodial repositories for derelicts, of which there are too many in existence today. Only thus can one give the right answer to divine scrutiny. Yes, we are our brothers' keepers.
433 Marlborough Street

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ards of health [and alleviation of suffering are equally vital, both from a practical point of view and from that of morale. All who took part in induction-board examinations during the war realize that the maintenance and development of national health is of as vital importance as the maintenance and development of armament.

The trend of development in the facilities available for the chronically ill outlined above will not necessarily be altered by public or state medicine. With provision of public funds in any setting of public activity the question is bound to come up, "Is it worth while to spend a certain amount of effort to restore a certain type of patient?" This rationalistic point of view has insidiously crept into the motivation of medical effort, supplanting the old Hippocratic point of view. In emergency situations, military or otherwise, such grading of effort may be pardonable. But doctors must beware lest such attitudes creep into the civilian public administration of medicine entirely outside emergency situations, because once such considerations are at all admitted, the more often and the more definitely the question is going to be asked, "Is it worth while to do this or that for this type of patient?" Evidence of the existence of such an attitude stared at me from a report on the activities of a leading public hospital unit, which stated rather proudly that certain treatments were given only when they appeared promising. "Our facilities are such that a case load of 20 patients is regularly carried in selecting cases for treatment careful consideration is given to the prognostic criteria, and in no instance have we instituted treatment merely to satisfy relatives or our own consciences." If only those whose treatment is worth while in terms of prognosis are to be treated, what about the other ones? The doubtful patients are the ones whose recovery appears unlikely, but frequently if treated energetically, they surprise the best prognosticators. And what shall be done during that long time lag after the disease has been called incurable and the time of death and autopsy? It is that period during which it is most difficult to find hospitals and other therapeutic organizations for the welfare and alleviation of suffering of the patient.

Under all forms of dictatorship the dictating bodies or individuals claim that all that is done is being done for the best of the people as a whole, and that for that reason they look at health merely in terms of utility, efficiency and productivity. It is natural in such a setting that eventually Hegel's principle that "what is useful is good" wins out completely. The killing center is the *reductio ad absurdum* of all health planning based only on rational principles and economy and not on humane compassion and divine law. To be sure, American physicians are still far from the point of thinking of killing centers, but they have arrived at a danger point

in thinking, at which likelihood of full rehabilitation is considered a factor that should determine the amount of time, effort and cost to be devoted to a particular type of patient on the part of the social body upon which this decision rests. At this point Americans should remember that the enormity of a euthanasia movement is present in their own midst. To the psychiatrist it is obvious that this represents the eruption of unconscious aggression on the part of certain administrators alluded to above, as well as on the part of relatives who have been understandably frustrated by the tragedy of illness in its close interaction upon their own lives. The hostility of a father erupting against his feeble-minded son is understandable and should be considered from the psychiatric point of view, but it certainly should not influence social thinking. The development of effective analgesics and pain-relieving operations has taken even the last rationalization away from the supporters of euthanasia.

The case, therefore, that I should like to make is that American medicine must realize where it stands in its fundamental premises. There can be no doubt that in a subtle way the Hegelian premise of "what is useful is right" has infected society, including the medical portion. Physicians must return to the older premises, which were the emotional foundation and driving force of an amazingly successful quest to increase powers of healing and which are bound to carry them still farther if they are not held down to earth by the pernicious attitudes of an overdone practical realism.

What occurred in Germany may have been the inexorable historic progression that the Greek historians have described as the law of the fall of civilizations and that Toynbee¹⁸ has convincingly confirmed—namely, that there is a logical sequence from *Koros* to *Hybris* to *Ate*, which means from surfeit to disdainful arrogance to disaster, the surfeit being increased scientific and practical accomplishments, which, however, brought about an inclination to throw away the old motivations and values by disdainful arrogant pride in practical efficiency. Moral and physical disaster is the inevitable consequence.

Fortunately, there are developments in this democratic society that counteract these trends. Notable among them are the societies of patients afflicted with various chronic diseases that have sprung up and are dedicating themselves to guidance and information for their fellow sufferers and for the support and stimulation of medical research. Among the earliest was the mental-hygiene movement, founded by a former patient with mental disease. Then came the National Foundation for Infantile Paralysis, the tuberculosis societies, the American Epilepsy League, the National Association to Control Epilepsy, the American Cancer Society, The American Heart Association, "Alcoholics Anony-

microscopical examination by the pathologist. The first step depends on the physician. He must be able to see the lesion clearly (this often is not easy at the far end of a bronchoscope or sigmoidoscope). On the other hand, since early carcinoma of the cervix may present no visible changes, one must rub the sponge over the area in which these lesions begin, the ring of the external os, the adjacent portion of the lips of the cervix and the adjacent lower cervical canal. When a visible lesion presents a

sections may also be taken. The pathologist can quickly familiarize himself with the findings in sponge biopsy by rubbing sponges over fresh tumors immediately after removal from the patient. Sections from such sponges will show the ease with which cancerous material may be absorbed by a suitable sponge and demonstrated on microscopical examination.

CASE REPORTS

CASE 1 C. J. (8125-48), a 40-year-old married woman, reported to the New York Polyclinic Outpatient Department on May 24, 1948, complaining of backache of 2 years duration.

The patient had 2 children, 13 and 16 years of age. The past history showed pneumonia in 1926. The menstrual periods were regular, occurring every 28 days and lasting for 4 days. No irregularities in menstrual bleeding, no dysmenorrhea and no spotting had been noticed.

Physical examination disclosed a slightly overweight, well developed woman. Examination of the head, neck, chest and abdomen revealed no abnormalities. On pelvic examina-



FIGURE 2 Second Sponge Biopsy in Case 1

High-power photomicrograph showing one of the particles of cancer tissue embedded in the sponge. The gelatin sponge is seen to the left. The tumor-cell nuclei are large and darkly staining, with marked variation in size and shape.

grayish-white necrotic base, the dead tissue must be removed by gauze before the diagnostic sponge is applied. The success of the method depends more than anything else upon the ability to reach the lesion, and to rub the sponge firmly over it. The technician should embed the sponge so as to cut sections from the flat surface usually discolored after having been rubbed over the ulcer. If tiny particles of tissue are seen in the formalin bottle, they should be processed along with the sponge, and placed in contact with the sponge surface to be cut, before embedding. One may accomplish this by placing the tissue particles in the melted paraffin and then covering them with the sponge. The sections taken from the immediate surface of the paraffin block should be mounted. Deeper



FIGURE 3 Surgical Specimen in Case 1 (Low-Power Photomicrograph of the Cervix)

The plane of the section is perpendicular to the axis of the cervical canal just above the external os. Note the thick layer of darkly staining cells, with finger-like projections into the underlying tissue. Filling, destruction and replacement of mucous glands by the advancing growth are seen.

tion a Bartholin-gland cyst, left side, and a retroverted uterus were found. The cervix uteri on direct visual inspection through a bivalve speculum appeared normal.

The temperature was 99.2°F, the pulse 80, and the respirations 20. The blood pressure was 148/80.

Examination of the blood showed a red-cell count of 4,730,000, with a hemoglobin of 90 per cent (Sahli). The sedimentation rate was 5 mm in 1 hour. The urine was clear, with a negative test for sugar and a faint trace of albumin.

DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX BY SPONGE BIOPSY*

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NEW YORK CITY

SINCE cancer in its early stage is a localized lesion, successful treatment depends on complete surgical removal of the diseased tissue or its complete destruction by adequate radiation. The diagnosis of cancer by the recognition and proper

its ready accessibility provides an ideal site for the detection of early carcinoma prior to the onset of signs, symptoms or anatomic changes visible on clinical inspection. Two such cases diagnosed by the method of sponge biopsy^{1,2} and treated by hysterectomy are reported below.

METHOD

The method of sponge biopsy depends on the absorption of fluid, cells and tissue particles from the surface of an ulcer or mucous membrane rubbed by an absorbing sponge of suitable structure and chemical composition. The sponge and absorbed contents are fixed in formalin, embedded in paraffin, sectioned by microtome and stained with hematoxylin and eosin. The stained paraffin sections are then examined by a qualified pathologist for the presence of tumor cells and fragments of tumor tissue.

A suitable sponge must be of such chemical composition as to withstand the solvent action of alcohol, chloroform, acetone or other fluids used in tissue preparation. For this purpose we have worked mostly with gelfoam No. 12 (Upjohn). A flat square of sponge 2.0 by 2.0 by 0.5 cm. is clamped along one margin by a surgical sponge forceps. The ulcer is wiped clean with dry sterile gauze, and then the dry diagnostic sponge is rubbed gently over the suspected area. After the sponge becomes wet, it is pressed more firmly between the tissue and the sponge holder, with slight rubbing. Each of the two sponge surfaces is thus brought into contact with the area to be examined, to permit later sectioning from either surface after embedding in paraffin. The flat sponge is used for rubbing of the surface of the cervix uteri, or lesions of the skin, mouth, lower rectum and so forth. When working through a long tube such as a sigmoidoscope, one may employ a small piece of sponge at the end of a uterine forceps. This is also useful for insertion into the external os of the cervix uteri. In bronchoscopy, a special narrow sponge holder is chosen.

To ensure the absorption of an adequate amount of material it is best to rub the sponge around the edge of the ulcer near the surrounding normal tissue. Also, the outside surface of the metal ring of the sponge holder may be filed to produce several radial grooves. These will help to dislodge tiny particles from the ulcer.

The method depends for its success in the first place on the actual transfer of cancerous tissue from the lesion to the sponge, secondly, on the proper preparation of sections and, thirdly, on the recognition of cancerous material in the slide during



FIGURE 1 First Sponge Biopsy in Case 1

High-power photomicrograph, demonstrating irregular broad band of gelatin sponge to the left and below. In the center and below are two particles of cancer tissue made up of large cells with large, darkly staining, irregular nuclei, showing marked variation in size and shape.

interpretation of early clinical signs and symptoms is in several important categories wholly inadequate, as witnessed by the poor results in the treatment of gastric and bronchogenic carcinoma. In lesions of the stomach and lung the symptoms appear and the diagnosis is made at a stage of the disease in which the cancer most often has advanced beyond the possibility of complete removal. For successful treatment in such cases, the detection of the disease will have to be made *before* the onset of clinical complaints. The cervix uteri because of

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About 2 weeks later surgical biopsy in the form of curettings from the external os was done. The pathologist's report was as follows:

The specimen consists of several small fragments of soft red and brown tissue aggregating in all about 0.2 cc. Microscopical examination shows hyperplasia of large undifferentiated epithelial cells in thick layers. The tissue appears coagulated. There is a tendency to concentric formations. Groups of cells that stain more clearly demonstrate large nuclei darkly staining with considerable variation in size and shape. The basement membrane is indistinct and in part is traversed by the growing cells. The diagnosis is epidermoid carcinoma of the cervix.

A month after the cervical os was curetted a complete hysterectomy with bilateral salpingo-oophorectomy was performed. The pathological report was as follows:

The specimen consists of a uterus with both tubes and ovaries attached. The cervix has been incised along the posterior wall. The specimen is fixed in formalin. The uterus measures 9 by 6 by 5 cm. On section the uterine wall measures 2 cm in thickness. The endometrium measures about 3 mm. The lips of the cervix are reddish brown. The surface is somewhat irregular and the external os has a granular appearance. The cervical canal is pale gray. The endometrium is reddish brown. On the lip of the cervix between the os and the circumference in the lower right-hand quadrant there is an ulcerated grayish-brown area 7 mm in diameter. On section the underlying tissue shows the extension of pearly white tissue from the surface, reaching about 5 to 8 mm into the depths. The ovaries feel somewhat firm and measure 2.5 to 3.0 cm in length.

Microscopical examination of the ulcerated area of the cervical lip described in the gross shows an abundant growth of large atypical tumor cells, epidermoid in type, extending in cords and irregular masses into the underlying muscular tissue (Fig. 6). There is considerable necrosis, fibrosis and lymphocytic infiltration between and around the masses of tumor tissue. Surrounding the tumor growth are numerous dilated, thin-walled blood vessels. Between the ulcer and the cervical os the epithelial zone is thickened and made up of large vesicular, anaplastic cells, many containing large nuclei and distinct nucleoli. Irregular masses of invasive tumor tissue are also seen in the area of the external os. The abnormal epithelial growth extends also in the opposite direction over the cervical lip, and at one point makes an abrupt transition to normal epithelium. The latter shows the oblique line often described. In cut sections the hyperplastic surface growth extends down into the mucous glands filling, destroying and replacing them. The individual cells are markedly atypical. The endometrial glands show slight hyperplasia. The myometrium appears normal. In the ovary there are several corpora albicantia and considerable hyperemia. The diagnosis is epidermoid carcinoma of the cervix.

Review of this case indicated that the tissue obtained by surgical biopsy consisted of anaplastic superficial growth. The more differentiated and more characteristic epidermoid type of cancer tissue was confined to the invasive area on the lip. This area was not detectable on clinical inspection. It was missed on surgical biopsy. Sponge biopsy, however, gathered from its surface characteristic cells and tissue particles.

DISCUSSION

Of the 2 cases of cancer of the cervix reported the first was superficial or intraepithelial. The second was similar except that in one area a small invasive tumor mass, 0.8 cm in greatest diameter, had developed. The incidence of early, superficial or intraepithelial cancer of the cervix varies

somewhat according to the specimens or patients studied and the methods used for obtaining material for biopsy. In a study of 1200 whole cervixes, most of which were from patients on whom hysterectomies had been performed, Pund and Auerbach⁴ observed 47 cases of preinvasive carcinoma (almost 4 per cent). TeLinde and Galvin⁵ by the use of surgical biopsy, found 8 early cancers in 704 cases. Foote and Stewart⁶ reported the collection of 27 pathological specimens of intraepithelial carcinoma of the cervix in the Memorial Hospital laboratory.



FIGURE 6 Case 2 Surgical Specimen from Cervix Uteri. A very low-power photomicrograph, showing invasiveness of cancer with destruction of underlying tissue.

during a period of three years. The three reports mentioned demonstrate the frequency of these lesions and indicate the importance of detecting them. Foote and Stewart, by serial sections, demonstrated the precise location of these lesions at the cervical os, cervical canal and cervical lips. These areas are readily accessible to the diagnostic sponge for the collection of tissue for microscopic examination.

SUMMARY

Two cases of early asymptomatic carcinoma of the cervix diagnosed by sponge biopsy are reported. The first case was superficial and intraepithelial. The second was similar but included one invasive area 0.8 cm in greatest diameter. The frequency

Microscopical examination of the sediment demonstrated an occasional white cell and red cell, with no casts. A cervical smear was negative for gonococci.

On October 14 a sponge biopsy was performed by rubbing of a flat piece of sponge over the cervix uteri visualized through the speculum. A longitudinal piece of sponge held at the end of a uterine clamp was inserted into the cervical canal. The sponges were treated and examined in the manner described above. The report of the sponge biopsy was as follows:

Microscopical examination of the sponge from the cervical canal shows clumps of large atypical epithelial tumor cells. A small particle of tissue (Fig 1) is made up of large, darkly staining epithelial cells, with large nuclei, showing marked atypism and variations in size and shape

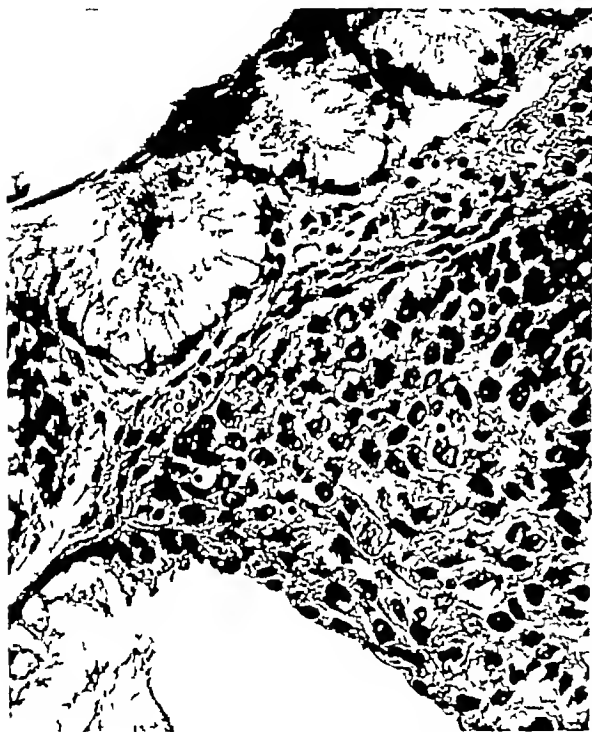


FIGURE 4 Surgical Specimen in Case 1 (High-Power Photomicrograph)

Cancer is present in the center and to the right, with intact, mucous glands above. The mucous gland below and to the left is partly destroyed by advancing tumor.

The large sponge rubbed over both lips of the cervix and external os shows abundant stratified squamous epithelium, as well as tiny particles of cancer tissue and individual cancer cells.

The sponge biopsy was repeated on October 28, and showed fragments of cancer tissue (Fig 2) in the sponge inserted into the cervical canal. Scattered cancer cells were found in the sponge rubbed over the lips and external os of the cervix.

On the basis of the sponge biopsy, a diagnosis of epidermoid carcinoma of the cervical canal was made, and a total hysterectomy and bilateral salpingo-oophorectomy were performed on November 6.

Pathological examination of the specimens revealed small ovarian cysts, the largest 2 cm in diameter. The tubes measured 8.0 x 0.6 cm and showed several serosal cysts. The uterus appeared normal in shape and measured 10 by 6 by 5 cm. The uterine wall varied from 1.5 to 2.5 cm in thickness. The mucosa of the cervical canal was thickened

near the external os up to about 4.0 mm. A small ulcer, 3 mm in diameter, was seen in this area. On cross section within the thickened mucosa, several pin-point, reddish spots were visible.

Microscopical examination was reported as follows:

There is moderate hyperplasia of the endometrial glands, with dilatation and cyst formation. The mucosa of the cervical canal is covered by a layer of closely packed, darkly staining cells (Fig 3), rather large, showing considerable variation in size and shape. The nuclei are also large and reveal occasional mitotic figures. At several points finger-like projections of this tissue extend into the underlying fibromuscular tissue and into the underlying mucous glands, several of which are partly destroyed and replaced by the invading growth (Fig 4). Also present are several dilated and cystic mucous glands. The epithelial surface covering the external os is intact. Beneath it are several mucous cysts. The diagnosis is epidermoid carcinoma of the cervix in situ.

CASE 1 D S, a 48-year-old woman whose vague complaints were thought to be of menopausal origin, was accordingly referred to a gynecologist for possible endocrine therapy. In the course of pelvic examination a sponge biopsy of the cervix uteri was performed. There were no visible abnormalities of the external os or lips of the cervix on direct inspection.



FIGURE 5 Sponge Biopsy in Case 2

High-power photomicrograph, showing a particle of cancer tissue embedded in the sponge. The cell nuclei are large and darkly staining, with marked variation in size and shape.

There were no abnormalities of menstruation, no abnormal bleeding and no spotting. The findings on sponge biopsy were reported as follows:

Microscopical examination discloses many large, darkly staining, atypical cells, with large nuclei showing marked variations in size and shape. Some cells have double nuclei. Small particles of tissue made up of atypical cells are also present (Fig 5). There is a moderate amount of blood. The findings are those of epidermoid carcinoma of the cervix. Confirmation by surgical biopsy is advisable prior to treatment.

About 2 weeks later surgical biopsy in the form of cuttings from the external os was done. The pathologist's report was as follows:

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FIGURE 6 Case 2 Surgical Specimen from Cervix Uteri
A very low-power photomicrograph, showing invasiveness of cancer with destruction of underlying tissue.

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SUMMARY

Two cases of early asymptomatic carcinoma of the cervix diagnosed by sponge biopsy are reported. The first case was superficial and intraepithelial. The second was similar but included one invasive area 0.8 cm in greatest diameter. The frequency

of these lesions varied from 1 to 4 per cent in the series cited

A cervix that looks normal on clinical visual inspection may be the site of early cancer. The two cases reported indicate the usefulness of sponge biopsy in obtaining tissue for microscopical examination in the diagnosis of early carcinoma of the cervix.

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DIHYDROSTREPTOMYCIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS*

With Particular Reference to Its Toxicity As Compared with That of Streptomycin

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SINCE September 1946 the United States Veterans Administration Hospital, Rutland Heights, Massachusetts, a 600-bed hospital for the treatment of veterans with tuberculosis, has been engaged in the study of streptomycin and its effect in controlling various forms of the disease. It is not within the province of this paper to discuss the results of these studies, which have been presented in previous reports.¹⁻⁶ In most cases streptomycin has not been considered to be definitive therapy, but rather a very helpful adjunct to other well established methods of treatment, such as bed rest and the various forms of collapse therapy, in the pulmonary cases, and bed rest alone, or in conjunction with surgical procedures, in the extrapulmonary cases. The latter group includes draining sinuses and tuberculosis of the bones, joints, lymph nodes, alimentary tract, kidneys and peritoneum.

The chief deterrents to the use of streptomycin are toxicity and the rapid emergence of resistant strains of the organism concerned, the *Mycobacterium tuberculosis*. Toxicity for the most part is a neurotoxicity directed against the eighth cranial nerve, particularly its vestibular branch, so that vestibular function is either impaired or lost. Important, but less so than the neurotoxic tendency of the drug, is the allergic reaction, whose chief manifestation is skin eruption. Much of the fear of toxicity has been allayed by shortening of the course of the drug and lessening of the daily dosage. Resistance of the tubercle bacillus to streptomycin is far from remedied and remains the bug-a-boo of the drug's true effectiveness.

To combat the toxicity, Merck and Squibb chemists have been working on various modifications of the original streptomycin with the result that there has emerged a closely related compound produced from crude streptomycin complex by hydrogenation, which has been called dihydrostreptomycin.

We have treated 20 patients with this new compound for ninety days.

The principal object of the study was to determine the toxicity of the drug, although its therapeutic properties have not been overlooked.

Following the *modus operandi* of all streptomycin studies carried out in Veterans Administration Hospitals, more carefully to anticipate and evaluate toxicity from the drug, numerous laboratory tests were carried out before treatment and at weekly intervals thereafter, unless otherwise specified. These procedures consisted of audiograms (done bi-weekly), caloric tests using ice water (done bi-weekly), urine analyses, complete blood counts, erythrocyte sedimentation rates (Cutler method), urea clearance, blood urea nitrogen, prothrombin times, stereoroentgenograms of the chest (monthly) and sputum concentrates for acid-fast bacilli (monthly). In addition to these tests, sensitivity studies were carried out and dihydrostreptomycin blood levels determined.

PREPARATION FOR INJECTION

The drug was received in 1-gm vials, and the material, a white powder, made a colorless clear solution, 4 cc of sterile distilled water was added to the vial, and 2 cc, equivalent to 0.5 gm of the drug, was injected at a dose, usually in the gluteal muscles. In the first few weeks of treatment, injections were given every four hours "around the clock" to the patients receiving 3 gm, and every four hours from 8 a m through 8 p m to those receiving 2 gm daily.

*From the Medical Service, Veterans Administration Hospital, Rutland Heights, Massachusetts. Published with permission of Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

†The dihydrostreptomycin used in this study was furnished by Merck and Company, Rahway, New Jersey.

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The first lots of the drug caused considerable irritating reaction at the site of injection. In addition, there were paresthesias in 6 patients manifested by numbness of the lips. When the study was about half completed, Dr. James Carlisle, medical director of the Merck Company, who had followed our work with interest, sent us some dihydrostreptomycin sulfate for trial, stating that it had been found less irritating in animals than the hydrochloride. We injected 0.5 gm of the sulfate in the left arms of the 20 patients and at the same time injected 0.5 gm of the hydrochloride in the right arms, without informing the patients of our experiment. With one exception all patients had pain, burning or soreness in the right arm and none in the left. The exception had pain in neither arm. We were then convinced that the dihydrostreptomycin hydrochloride was much more irritating than the dihydrostreptomycin sulfate, and since then we have used the sulfate when it was obtainable. Later in the study, injections were given as follows for the patients receiving 3 gm, 0.5 gm in each buttock three times a day, for those receiving 2 gm, 0.5 gm in each buttock twice a day, because injection of 1 gm at one site appeared to be too irritating.

CASES TREATED

Twenty patients with active pulmonary tuberculosis, including 1 with generalized miliary tuberculosis, were treated for ninety days. Half these received 2 gm of dihydrostreptomycin daily, and half 3 gm daily. The extent of the disease was advanced in all cases according to the classification of the National Tuberculosis Association, 18 were far advanced, 1 was moderately advanced, and 1 had generalized miliary tuberculosis. Fourteen patients (70 per cent) had cavity disease, 17 (85 per cent) had bilateral lung involvement, and 6 (30 per cent) had more than 50 per cent exudative disease as determined by roentgenograms. Nineteen patients had positive sputums. We were able to obtain positive cultures in 18 of these. The clinical and roentgenographic indication of a generalized miliary tuberculosis was so profound in 1 patient that treatment was given in spite of negative sputum smears and cultures. Subsequent events in this case confirmed our impression that the hematogenous infection was of tuberculous origin, tuberculous meningitis developed soon after completion of the course, the patient died, and autopsy confirmed the diagnosis. All but 1 of the patients were white men, the exception being a Negro forty-two years of age. The ages ranged from twenty-one to fifty-three, the majority being in the third and fourth decades.

TOXICITY

Subjective Symptoms

During the first week of treatment, aside from the tissue irritation, 6 patients complained of

paresthesias, for the most part involving the lips which were described as "numbness," "feeling of fullness" and "dead sensation" by various patients. One of these patients likewise complained of paresthesias involving the tip of the left thumb, index and middle finger, of forty-eight hours' duration. These paresthesias appeared within the first two days of treatment. They were of short duration in all cases, lasting from five minutes to forty-eight hours. The drug was not discontinued because of them. The paresthesias, having disappeared, did not return. At first it was believed they were manifestations of the neurotoxicity of dihydrostreptomycin. However, since they did not appear in any of the patients who subsequently received other lots of the drug, which presumably had been more purified, it is now believed that these early toxic manifestations were not due to the drug itself but to impurities in the early lots administered.

Two patients complained of gastrointestinal upsets during the course of treatment. 1 of nausea on the morning following institution of treatment, and the other of nausea, vomiting, chills and fever for two days during the third week of treatment. Whether the disturbance was an effect of the drug cannot be stated with certainty, since it may have been caused by a gastrointestinal infection unrelated to treatment.

Between the thirtieth and the forty-seventh day of treatment, 4 patients complained of tinnitus that was of transient duration but recurrent in two patients. This was not accompanied by impairment of hearing or audiometric changes of significant degree in any of the patients, so that the drug was not discontinued because of this symptom. One patient complained of slight dizziness and stated that he walked as though he had "blind staggers." This symptom appeared at the end of the fifth week of treatment. Actually the patient demonstrated little ataxia when he was observed getting out of bed and walking across the room. At that time, caloric tests were normal. On the sixtieth day of treatment, however, ataxia was definite, and the caloric test revealed almost complete loss of vestibular function. This patient received 3 gm of the drug daily. The drug was immediately stopped. No patients demonstrated clinical hypersensitivity to the drug as evidenced by skin eruptions, edema of the eyelids, bronchospasm or arthralgia. There were no cases of agranulocytosis or purpura.

Laboratory Evidence of Toxicity

Six patients (30 per cent) of the group of 20 showed eosinophil counts above 5 per cent. The counts were never higher than 8 per cent and usually appeared in the third and fourth weeks of treatment, returning to normal by the eighth week.

Evidence of renal impairment. Urinalyses were essentially normal in all but 2 cases. One of these patients had a single specimen that showed

many hyaline casts after two weeks of therapy, subsequent specimens were negative. Urine from the other patient showed many white cells and granular casts after four weeks and nine weeks of treatment. This patient's most recent urea clearance has shown a decided drop to 38 per cent, he is fifty-three years of age and has far advanced tuberculosis. Further studies to rule out renal tuberculosis are being performed. Blood urea nitrogen determinations have been normal.

Urea clearance tests showed no significant reduction except in the one case cited above. Blood urea nitrogen determinations were within normal limits in all cases.

There was no clinical evidence of liver damage in any of the patients, although tests of liver function were not carried out, except for a study of weekly prothrombin times in all cases. Prothrombin-time measurements varied through the weeks in most patients, but at no time showed any significantly marked rise or fall from the normal.

Hematologic evidence of toxicity. Red-cell counts were unchanged from pretreatment levels in 11 patients (55 per cent).

Because of the human element of error in counting red blood cells, we considered only deviations of 1,000,000 or more red cells to be significant, 45 per cent showed a drop of 1,000,000 cells after the first week of treatment. All these counts returned to their pretreatment level between the eighth and the twelfth week of treatment.

The photoelectric colorimeter was used for determinations of hemoglobin. Deviations of 5 per cent or more were recorded. Except for 3 patients, who demonstrated a slight fall in hemoglobin soon after treatment started, the determinations in the remaining patients either showed no significant deviation from pretreatment levels or became higher during the early weeks of treatment.

There was considerable variation in the white-cell and differential counts, but in no case was there a definite leukopenia or agranulocytopenia.

Erythrocyte sedimentation rates (Cutler method). Changes of 5 mm. or more from pretreatment readings were recorded. Five patients (25 per cent) demonstrated a fall to normal during the fifth to the tenth week of treatment. Eight (40 per cent) patients demonstrated a fall from pretreatment readings, but not to normal, between the fifth and the twelfth week of treatment. Seven patients demonstrated no change in their sedimentation rates during treatment. Six of these were elevated, and 1 was normal.

Caloric Tests

Bi-weekly caloric tests were carried out, a modified Kobrak technic, injecting 5 cc. of ice water in each ear, being used and the time of appearance of nystagmus and its duration being noted. During the ninety-day course only 1 patient of the

entire group showed any substantial loss in vestibular function.

Audiometric Tests

Bi-weekly audiograms were made on all patients. Only 1 patient revealed any impairment of cochlear-nerve function audiometrically during treatment, and this was slight. There was no clinical deafness.

CLINICAL OBSERVATIONS

In marked contrast to the feeling of well-being and increased appetite, which was striking in the great majority of patients treated with streptomycin, the present group of patients receiving dihydrostreptomycin experienced little benefit in this respect. In fact several patients complained of loss of appetite during the first few weeks of treatment. Euphoria in the group was conspicuous by its absence.

A gain in weight during treatment was observed in 15 patients (75 per cent). The weight of 1 patient remained stationary, and 4 patients (20 per cent) lost 3 pounds or less. Of those who gained, 4, or 20 per cent, showed a gain from 1 to 5 pounds, 3, or 15 per cent, gained from 5 to 10 pounds, and 8, or 40 per cent, gained over 10 pounds.

Seven patients were afebrile at the onset of dihydrostreptomycin therapy, and these patients continued afebrile throughout treatment. Of the 13 patients with fever, 7 reverted to normal, 1 after three days of therapy, 3 after three weeks of therapy, and the remainder in six to twelve weeks.

Eight patients showed pulse rates below 90 before treatment, and these rates did not change. One patient, whose rate ranged between 90 and 100 before treatment, maintained approximately the same slightly elevated rate. Eleven patients had rates persistently above 100 prior to treatment with the drug, 5 of these continued to have rates above 100 but lower than the pretreatment rates, in the other 6 the pulse rates were reduced to 90 or below. (All pulse rates recorded are the patient's usual late afternoon rates taken while he was on complete bed rest.)

Although cough and expectoration were not uniformly severe in this group, all patients showed moderate to marked reduction in the severity of the cough and lessened expectoration.

Nineteen patients had positive sputums prior to the institution of therapy. The twentieth patient was the case of generalized miliary tuberculosis described above. Three patients had sputums that were negative after two weeks to one month of dihydrostreptomycin therapy and were still negative at the completion of their course. In the other 16 the specimens were considered to be positive.

The roentgenograms of the patient with miliary tuberculosis cleared almost completely during treatment, but after completion of his course of therapy,

tuberculous meningitis developed and was confirmed by post-mortem examination

ROENTGENOGRAPHIC OBSERVATIONS

At the completion of the ninety-day course of the drug, 12 patients (60 per cent) showed improvement by x-ray study, however, half these cases showed only slight or minimal improvement. Seven patients (35 per cent) demonstrated no change on x-ray examination, and 1 patient (5 per cent) appeared worse.

Of the 12 patients whose x-ray films revealed improvement, 8 showed improvement after one month, 3 after two months, and 1 at the completion of treatment.

BLOOD LEVELS AND SENSITIVITY STUDIES

Concentration of Dihydrostreptomycin in Blood Serum

Dihydrostreptomycin blood levels were determined by the tube dilution method, *Staphylococcus aureus* (SM) being used as the test organism. Blood-level determinations were carried out on only 6 patients. A single determination was done on each patient. Blood for the tests was drawn within an hour of the administration of dihydrostreptomycin. At the time these tests were carried out, patients were being given single intramuscular injections of 1 gm twice daily, or three times daily, depending upon the regimen followed for their particular group.

The average one-hour blood level for a group of 3 patients receiving 3 gm of dihydrostreptomycin daily (three divided doses of 1 gm each) was found to be 42.6 microgm per cubic centimeter. The average one-hour blood level for a group of 3 patients receiving 2 gm of dihydrostreptomycin daily (two divided doses of 1 gm each) was found to be 20.7 microgm per cubic centimeter.

Determination of Dihydrostreptomycin Sensitivity of Tubercle Bacilli

Routine sensitivity determinations were performed with the use of a Dubos liquid medium containing varying concentrations of dihydrostreptomycin. Tubes with dihydrostreptomycin, as well as suitable controls, were inoculated with standard suspensions of five-day-old cultures of tubercle bacilli in a Dubos medium prepared from primary cultures grown on potato-egg-glycerin slants. Inoculated tubes were incubated at 37°C. Development of turbidity, indicating active growth of the tubercle bacilli, often could be noted within one or two days. A Coleman model 6 junior clinical spectrophotometer, measuring transmission of light at a wave length of 620 millimicrons, was used in these determinations. Final readings were not made before the fourteenth day of incubation, however.

To supplement the routine procedure described above, sensitivity determinations on recent speci-

mens have been carried out with a modified Herrold egg-yolk-agar solid medium with malachite green⁷ containing varying concentrations of dihydrostreptomycin. Utilization of this medium permits results of sensitivity determinations to be placed on a quantitative, as well as a qualitative, basis, since the ratio of resistant to sensitive tubercle bacilli in a given inoculum can be estimated readily by comparison of the amounts of growth in test cultures with that of the control culture.

Complete data on sensitivity tests for all twenty patients in this series are not available, since cultural studies on recently submitted specimens are still in progress.

As was expected, pretreatment cultures of tubercle bacilli obtained from 18 of the 20 patients were found to be sensitive to 1 microgm per cubic centimeter of dihydrostreptomycin. It has not been found possible thus far to demonstrate tubercle bacilli by cultural methods in sputum specimens obtained from the other 2 patients, 1 of whom was being included in the group that received 3 gm of dihydrostreptomycin daily, and the other in the group that received 2 gm daily.

Sufficient data have been accumulated to show that 4 patients of the 10 who received 3 gm of dihydrostreptomycin daily produced tubercle bacilli resistant to 100 (or more) microgm per cubic centimeter of dihydrostreptomycin within the first thirty to fifty days of therapy. One patient of the 10 who received 2 gm daily also demonstrated resistant tubercle bacilli. This was noted on the ninety-fourth day following institution of therapy and represented cultural data obtained from a post-treatment specimen. It is not possible to estimate more closely at what time resistance to dihydrostreptomycin developed since, inadvertently, no other specimens were submitted to the laboratory prior to the end of therapy.

By use of the modified Herrold medium, it was found that in each case in which resistance to dihydrostreptomycin had developed, 75 to 100 per cent of the culturally recoverable tubercle bacilli present in corresponding sputum specimens were resistant to at least 100 microgm per cubic centimeter of dihydrostreptomycin.

The sputum of a patient who received 3 gm of dihydrostreptomycin daily was positive by culture six weeks after termination of therapy. The culture proved sensitive to less than 1 microgm per cubic centimeter of dihydrostreptomycin. Incomplete studies on 2 other patients of this series show that 1 patient's culture was sensitive at the thirty-eighth day, and the other on the seventy-second day of treatment. Incomplete studies on 4 patients who received 2 gm daily show that cultures were still sensitive at the end of eighty-five, eighty-three, sixty-three and fifty-three days of treatment, respectively. No post-treatment data for this group are available.

many hyaline casts after two weeks of therapy, subsequent specimens were negative. Urine from the other patient showed many white cells and granular casts after four weeks and nine weeks of treatment. This patient's most recent urea clearance has shown a decided drop to 38 per cent, he is fifty-three years of age and has far advanced tuberculosis. Further studies to rule out renal tuberculosis are being performed. Blood urea nitrogen determinations have been normal.

Urea clearance tests showed no significant reduction except in the one case cited above. Blood urea nitrogen determinations were within normal limits in all cases.

There was no clinical evidence of liver damage in any of the patients, although tests of liver function were not carried out, except for a study of weekly prothrombin times in all cases. Prothrombin-time measurements varied through the weeks in most patients, but at no time showed any significantly marked rise or fall from the normal.

Hematologic evidence of toxicity. Red-cell counts were unchanged from pretreatment levels in 11 patients (55 per cent).

Because of the human element of error in counting red blood cells, we considered only deviations of 1,000,000 or more red cells to be significant, 45 per cent showed a drop of 1,000,000 cells after the first week of treatment. All these counts returned to their pretreatment level between the eighth and the twelfth week of treatment.

The photoelectric colorimeter was used for determinations of hemoglobin. Deviations of 5 per cent or more were recorded. Except for 3 patients, who demonstrated a slight fall in hemoglobin soon after treatment started, the determinations in the remaining patients either showed no significant deviation from pretreatment levels or became higher during the early weeks of treatment.

There was considerable variation in the white-cell and differential counts, but in no case was there a definite leukopenia or agranulocytopenia.

Erythrocyte sedimentation rates (Cutler method). Changes of 5 mm or more from pretreatment readings were recorded. Five patients (25 per cent) demonstrated a fall to normal during the fifth to the tenth week of treatment. Eight (40 per cent) patients demonstrated a fall from pretreatment readings, but not to normal, between the fifth and the twelfth week of treatment. Seven patients demonstrated no change in their sedimentation rates during treatment. Six of these were elevated, and 1 was normal.

Caloric Tests

Bi-weekly caloric tests were carried out, a modified Kobrak technic, injecting 5 cc of ice water in each ear, being used and the time of appearance of nystagmus and its duration being noted. During the ninety-day course only 1 patient of the

entire group showed any substantial loss in vestibular function.

Audiometric Tests

Bi-weekly audiograms were made on all patients. Only 1 patient revealed any impairment of cochlear-nerve function audiometrically during treatment, and this was slight. There was no clinical deafness.

CLINICAL OBSERVATIONS

In marked contrast to the feeling of well-being and increased appetite, which was striking in the great majority of patients treated with streptomycin, the present group of patients receiving dihydrostreptomycin experienced little benefit in this respect. In fact several patients complained of loss of appetite during the first few weeks of treatment. Euphoria in the group was conspicuous by its absence.

A gain in weight during treatment was observed in 15 patients (75 per cent). The weight of 1 patient remained stationary, and 4 patients (20 per cent) lost 3 pounds or less. Of those who gained, 4, or 20 per cent, showed a gain from 1 to 5 pounds, 3, or 15 per cent, gained from 5 to 10 pounds, and 8, or 40 per cent, gained over 10 pounds.

Seven patients were afebrile at the onset of dihydrostreptomycin therapy, and these patients continued afebrile throughout treatment. Of the 13 patients with fever, 7 reverted to normal, 1 after three days of therapy, 3 after three weeks of therapy, and the remainder in six to twelve weeks.

Eight patients showed pulse rates below 90 before treatment, and these rates did not change. One patient, whose rate ranged between 90 and 100 before treatment, maintained approximately the same slightly elevated rate. Eleven patients had rates persistently above 100 prior to treatment with the drug, 5 of these continued to have rates above 100 but lower than the pretreatment rates, in the other 6 the pulse rates were reduced to 90 or below. (All pulse rates recorded are the patient's usual late afternoon rates taken while he was on complete bed rest.)

Although cough and expectoration were not uniformly severe in this group, all patients showed moderate to marked reduction in the severity of the cough and lessened expectoration.

Nineteen patients had positive sputums prior to the institution of therapy. The twentieth patient was the case of generalized miliary tuberculosis described above. Three patients had sputums that were negative after two weeks to one month of dihydrostreptomycin therapy and were still negative at the completion of their course. In the other 16 the specimens were considered to be positive.

The roentgenograms of the patient with miliary tuberculosis cleared almost completely during treatment, but after completion of his course of therapy,

tuberculous meningitis developed and was confirmed by post-mortem examination

ROENTGENOGRAPHIC OBSERVATIONS

At the completion of the ninety-day course of the drug, 12 patients (60 per cent) showed improvement by x-ray study, however, half these cases showed only slight or minimal improvement. Seven patients (35 per cent) demonstrated no change on x-ray examination, and 1 patient (5 per cent) appeared worse.

Of the 12 patients whose x-ray films revealed improvement, 8 showed improvement after one month, 3 after two months, and 1 at the completion of treatment.

BLOOD LEVELS AND SENSITIVITY STUDIES

Concentration of Dihydrostreptomycin in Blood Serum

Dihydrostreptomycin blood levels were determined by the tube dilution method, *Staphylococcus aureus* (SM) being used as the test organism. Blood-level determinations were carried out on only 6 patients. A single determination was done on each patient. Blood for the tests was drawn within an hour of the administration of dihydrostreptomycin. At the time these tests were carried out, patients were being given single intramuscular injections of 1 gm twice daily, or three times daily, depending upon the regimen followed for their particular group.

The average one-hour blood level for a group of 3 patients receiving 3 gm of dihydrostreptomycin daily (three divided doses of 1 gm each) was found to be 42.6 microgm per cubic centimeter. The average one-hour blood level for a group of 3 patients receiving 2 gm of dihydrostreptomycin daily (two divided doses of 1 gm each) was found to be 20.7 microgm per cubic centimeter.

Determination of Dihydrostreptomycin Sensitivity of Tubercle Bacilli

Routine sensitivity determinations were performed with the use of a Dubos liquid medium containing varying concentrations of dihydrostreptomycin. Tubes with dihydrostreptomycin, as well as suitable controls, were inoculated with standard suspensions of five-day-old cultures of tubercle bacilli in a Dubos medium prepared from primary cultures grown on potato-egg-glycerin slants. Inoculated tubes were incubated at 37°C. Development of turbidity, indicating active growth of the tubercle bacilli, often could be noted within one or two days. A Coleman model 6 junior clinical spectrophotometer measuring transmission of light at a wave length of 620 millimicrons, was used in these determinations. Final readings were not made before the fourteenth day of incubation, however.

To supplement the routine procedure described above, sensitivity determinations on recent speci-

mens have been carried out with a modified Herrold egg-volk-agar solid medium with malachite green⁷ containing varying concentrations of dihydrostreptomycin. Utilization of this medium permits results of sensitivity determinations to be placed on a quantitative, as well as a qualitative, basis, since the ratio of resistant to sensitive tubercle bacilli in a given inoculum can be estimated readily by comparison of the amounts of growth in test cultures with that of the control culture.

Complete data on sensitivity tests for all twenty patients in this series are not available, since cultural studies on recently submitted specimens are still in progress.

As was expected, pretreatment cultures of tubercle bacilli obtained from 18 of the 20 patients were found to be sensitive to 1 microgm per cubic centimeter of dihydrostreptomycin. It has not been found possible thus far to demonstrate tubercle bacilli by cultural methods in sputum specimens obtained from the other 2 patients, 1 of whom was being included in the group that received 3 gm of dihydrostreptomycin daily, and the other in the group that received 2 gm daily.

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Supported by the data presented above there appears to be a trend showing that the resistance to dihydrostreptomycin develops in direct proportion to the size of the dosage used in therapy.

Though no final conclusions can be reached on the basis of the foregoing partially complete studies, it seems probable that the regimen consisting of intramuscular administration of 3 gm of dihydrostreptomycin daily for a period of ninety days will result in a higher percentage of cases resistant to dihydrostreptomycin than a similar regimen of 2 gm daily.

DISCUSSION

Nineteen patients with pulmonary tuberculosis and 1 with generalized miliary tuberculosis have been treated with dihydrostreptomycin. Ten patients received 2 gm of the drug daily, and 10 received 3 gm daily, for a period of ninety days. It was the main purpose of our study to evaluate any toxicity that the drug might possess in the dosage given. Accordingly, numerous laboratory tests were carried out at regular intervals, for the most part at weekly intervals. We also evaluated subjective symptoms and signs indicative of toxicity. The early symptoms of paresthesias in 6 patients, at first thought to be evidences of neurotoxicity of the drug, now appear to be evidences of impurities in the first lots of drug administered, since subsequent lots failed to produce these symptoms. Tinnitus, which developed in 4 patients, may well have been a true neurotoxic manifestation, since this symptom appeared later in the course of treatment. Audiometric observations were little changed from pretreatment readings. The nausea reported in 2 patients was an early symptom and may or may not have been significant. It does not appear to be a characteristic toxic manifestation of either dihydrostreptomycin or streptomycin. Since 1 patient receiving 3 gm daily practically lost vestibular function, and had to be dropped from the course on the sixtieth day, this demonstrates the possibility of specific toxic effects on the vestibular nerve.

Compared with streptomycin in similar dosage, vestibular-nerve toxicity appears considerably less in this group receiving dihydrostreptomycin. In our previous studies with streptomycin, of our original group of 20 patients receiving 1.8 gm for a hundred and twenty days, 75 per cent lost vestibular function by the end of the course, and most of these had lost function by the end of sixty days. In our

subsequent group of 31 patients who received 2 gm of streptomycin for sixty days, 64 per cent completely lost vestibular function.

Eosinophilia, which was common in our series of patients receiving various dosages of streptomycin, occurred with much less frequency in the present group of dihydrostreptomycin-treated patients. For example, 30 per cent of the latter showed eosinophil counts from 5 to 8 per cent, whereas 75 per cent of the former had counts that reached an upper limit of 17 per cent. This is consistent with the lessened toxicity observed in the present study.

Renal damage has not been observed in our study, and no evidence of renal irritation has been noted except in 1 case, in contrast to 40 to 50 per cent who received 1.8 gm of streptomycin and showed frequent albuminuria and cylindruria—not in themselves evidences of renal damage but certainly of probable renal irritation.

There has been no lasting effect of the drug on the hematopoietic system.

Prothrombin times were not altered significantly during treatment. No other liver-function tests were done, but no patient appeared to develop clinical evidence of liver damage.

Improvement was manifested by weight gain, lessened cough and expectoration, and disappearance of fever in all patients.

True evaluation of conversion of sputum cannot be made in this series since the time of observation is too short. At least three months of negative sputum should be required before one can consider a conversion definite.

Erythrocyte sedimentation rates were significantly lowered in 65 per cent of the group during treatment. This incidence is scarcely different from the decreases in the sedimentation rates that occurred in 75 per cent of 20 patients who received 1.8 gm streptomycin for a hundred and twenty days.

Roentgenographic improvement was observed in 60 per cent, and half of these patients showed only slight or minimal improvement. This is in contrast with the first group receiving 1.8 gm of streptomycin for a hundred and twenty days, who showed roentgenographic improvement at the end of ninety days of treatment in 75 per cent. In a series of 31 patients receiving 2 gm of streptomycin for sixty days, 90 per cent showed improvement. In a group of 13 patients receiving 1 gm of streptomycin for a hundred and twenty days, 84 per cent showed improvement by roentgenograms.

Therefore, not only the incidence of improvement but also the degree of improvement in the individual cases appeared less with dihydrostreptomycin.

CONCLUSIONS

From the observations in this group of 20 patients treated with intramuscular injections of 2 and 3 gm of dihydrostreptomycin daily for ninety days it is concluded that, in this dosage, the drug is less toxic than streptomycin in similar dosage.

The 2 patients showing the more serious evidences of toxicity, loss of vestibular function in 1 and renal irritation in the other, received 3 gm of the drug daily.

Our observations indicate that dihydrostreptomycin in the dosage given may be less effective therapeutically than streptomycin given in similar or smaller dosage.

Resistance studies are completed and available on only 12 patients in the group at this writing, 5 of whom developed resistant organisms during treatment.

Addendum—Because of the development of cochlear-nerve damage in 4 of the 20 cases reported subsequent to completion of the course of therapy, a brief description of the development of symptoms is important.

Follow-up study on the patient with ataxia on the sixtieth day of treatment, described above reveals that he has no residual dizziness or ataxia but vestibular function as interpreted by the caloric test has not returned. One week after discontinuation of therapy tinnitus developed and this has become slowly more marked. This patient's audiogram was not quite so good after sixty days of therapy as it was before treatment, and it has become slightly worse though progressively so, for five months.

The second patient, a fifty-two-year-old man received 2.0 gm of dihydrostreptomycin daily for ninety days. One month after completion of his course of treatment he complained of moderate tinnitus which has remained unchanged to the present (three months after treatment). Concomitantly he complained of occasional staggering and loss of balance when bending over, these symptoms being exaggerated in the dark. No deafness was noted, but at the onset of tinnitus slight impairment of hearing was shown by the audiogram.

The third patient, a thirty-year-old man, received 3.0 gm of dihydrostreptomycin daily for a period of ninety days.

There was no evidence of cochlear-nerve involvement until two months after treatment, and since then he has had occasional tinnitus and some clinical impairment of hearing. His audiogram also showed some impairment of function at the time tinnitus developed.

The fourth patient, a thirty-seven-year-old man, received 3.0 gm of dihydrostreptomycin daily for ninety days. One month after treatment marked tinnitus and mild deafness developed, both of which increased markedly in severity for the following month. An audiogram taken at the onset of tinnitus showed impairment of function. The audiogram taken a month later showed increased impairment.

In addition to these cases a patient came to us after receiving dihydrostreptomycin for about two months in another hospital. Because he had miliary disease, we decided to continue antibiotic therapy but changed to 2.0 gm of streptomycin daily. About a month after admission to this hospital (a month after dihydrostreptomycin had been stopped), he began to complain of deafness, and during the next month he became almost totally deaf.

We must add therefore to our discussion and conclusions, that in this admittedly small series of 20 cases, 4, or 20 per cent suffered cochlear-nerve damage, which became apparent only after dihydrostreptomycin therapy was completed. In 3 of these cases nerve damage was not apparent until at least a month after completion of treatment.

Though streptomycin is a definite toxin to the eighth nerve it more specifically attacks the vestibular branch, and much less often the cochlear division. Dihydrostreptomycin, on the other hand, appears to attack the cochlear division as frequently as the vestibular division of the eighth nerve, and much more often than streptomycin does.

We therefore believe that dihydrostreptomycin, in the dosage used at this hospital, is not the innocuous drug that we hoped it would be.

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FRACTURES OF THE DISTAL END OF THE RADIUS COMPLICATED BY FRACTURES OF THE CARPAL SCAPHOID

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THERE is a teaching that a fall on the outstretched hand may cause either a Colles fracture or a fractured carpal scaphoid, the latter usually occurring in young adults and the former in older people^{1,2}. Most of the literature ignores the possibility of both simultaneously. Our recent experience shows that the combination of the two fractures is a difficult problem that occurs in a significant number of cases and through a wide age range. Scudder,³ Brittain,⁴ Kev,⁵ Cleveland⁶ and other authors have stated that fractures of the distal end of the radius and of the carpal scaphoid can occur simultaneously at the same injury. Most of these authorities have considered the combination rare, and none discuss its frequency or its treatment. The mechanism of both injuries is nearly always the same — a fall on the outstretched hand. Force against the scaphoid and radius is indirectly applied either through the first metacarpal and the greater multangular,⁶ or through the second and third metacarpals and the capitate.² These bones may also be simultaneously fractured.^{6,7} Dickinson and Shannon,⁸ reporting 257 scaphoid fractures in soldiers whose average age was twenty-eight years, found 3 associated fractures of the radial styloid and 2 fractures of the shaft of the radius (the level of the fracture unspecified). Kellam and McGoe,⁹ reporting from a Canadian Army hospital, found that of 331 successive fractures of the radius and ulna, at all levels, 7 per cent of patients had carpal injuries, and that 10 per cent with injuries of the distal third of the radius had coincidental lesions of the carpus. No breakdown as to the specific carpal bone or the type of radial fracture is available, but in all probability the majority of the carpal injuries were fractures of the scaphoid.

An analysis of our wrist fractures for about six months shows that the combination is not uncommon, and that difficult problems of both diagnosis and treatment are met.

ANALYSIS OF CASES

Three hundred consecutive cases of recent fracture of the distal 5 cm of the radius of all types were studied. These cases were seen between September, 1946, and April, 1947. Twenty of the 300 patients, or 6.6 per cent, had associated fractures of the carpus. Of these, 15, or 5 per cent, had fractures of the body (either waist or proximal

pole) of the scaphoid, 2 had fractures of the triquetrum, and there were 1 each of the lunate, capitate and greater multangular.

The combination of radial and scaphoid fractures occurred over a wide age range. The youngest patient was fifteen, and the oldest, seventy-nine. The average age was forty-four and seven-tenths years. More than half the cases were in males. Ten of the 15 patients had radial fractures of the Colles type. 1 was impacted without displacement, 5 had backward tilting of the distal fragment, and 4 had comminuted "T" fractures involving the joint. Of the remaining 5, 3 had a chauffeur fracture of the radial styloid, 1 had a Barton fracture of the dorsal articulating surface, and there was 1 epiphyseal fracture with wide displacement of the distal epiphysis and a dorsal metaphyseal fragment. All these cases resulted from a fall on the outstretched hand except for the fractures of the radial styloid, which occurred from blows forcing the hand into dorsal and radial flexion. One case, similar to that of Cleveland,⁶ had associated fractures of the greater multangular, the scaphoid and the radius (Colles type). Another case (Fig 1) illustrates a different line of force, with fractures of the base of the third metacarpal, the waist of the scaphoid and a comminuted Colles fracture involving the joint. This case required four and a half months of immobilization for bony union to occur in the scaphoid.

DIAGNOSTIC PROBLEM

It is hard enough to diagnose a fracture of the scaphoid when the radius is not broken. A case with separation of the scaphoid fragments presents no diagnostic difficulty, but the barely visible hairline, which may not develop until many days after injury, is a more serious problem. The pain and swelling of the radial fracture mask the signs and symptoms referable to the scaphoid, and the surgeon is apt to see at a glance the gross deformity of the radius without bothering to look farther for a suspicious hairline in the scaphoid. It is very easy to concentrate attention on the radius to the exclusion of the carpus in check x-ray films, in which oblique views are seldom required. A policy of taking frequent careful scaphoid series is the only program that can prevent most errors.^{2,6,8}

THERAPEUTIC PROBLEM

None of the authors who discuss the occurrence of fractures of the scaphoid complicated by a comminuted Colles fracture mention the paradox of

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treatment that confronts the surgeon. Dorsiflexion with radial deviation is commonly accepted for treatment of the fractured scaphoid^{2 5 10 12} but ulnar deviation with volar flexion of the wrist is generally required for treatment of the Colles fracture with a tendency to slip after reduction. Any attempt to compromise may be unfortunate, non-union of the scaphoid and malunion of the radius being equally undesirable. Fortunately, this dilemma is not always encountered. A chauffeur fracture associated with scaphoid fractures may be treated for the scaphoid alone, especially since dorsal and radial flexion of the wrist relaxes the brachioradialis pull, preventing displacement of the radial styloid. Some Colles fractures and nearly all epiphyseal fractures of the distal radius are stable after reduction and can be immobilized in slight cockup or neutral position with radial deviation. They should, however, be followed very carefully to prevent or treat a change in position. When a cockup plaster gauntlet was used from the start in 5 favorable cases, healing took place within five to eight weeks. The method of Soto-Hall^{10 11} was used for fixation, except that the distal joint of the thumb was left free.

Most displaced Colles fractures cannot be held in dorsiflexion, however, and we have immobilized these in volar and ulnar flexion, changing the position to 20 to 30° of cockup in three or four weeks. This is very similar to the treatment of the scaphoid fracture associated with luxation of the lunate, since the lunate may also dislocate in a position of dorsiflexion.¹¹ Speed¹³ and Cravener and McElroy¹⁴ treated scaphoid fractures successfully in volar and radial flexion, although they do not recommend it now. We have treated the radius first because it heals first, with the important addition that the proximal phalanx of the thumb was included in the cast to prevent motion of the scaphoid fragments. This is easily done with a small amount of plaster, and prevents local resorption and cystic changes, which otherwise occur in a cast for the Colles fractures if the scaphoid fracture is not suspected. Six cases so treated have required nine to twenty weeks of immobilization for union to occur, and have needed extensive physiotherapy thereafter.

In 2 elderly patients of the series, in whom marked osteoporosis and vascular changes developed, active motion and physiotherapy were considered to be more important to the functional result than immobilization until bony union eventuated. Accordingly, after five or six weeks, casts were omitted and physiotherapy begun. We lost track of 2 other cases. Unfortunately, the follow-up study on all cases is not complete enough to warrant final conclusions of the best method of treatment.

SUMMARY AND CONCLUSIONS

Three hundred consecutive, recent fractures of the distal radius were complicated by fracture of the carpal scaphoid in 15 cases (5 per cent). The combination cannot be considered a rarity.

Diagnosis of the scaphoid fracture is difficult in presence of a radial fracture that dominates the x-ray picture and masks symptoms due to the fractured scaphoid.

Treatment of the combination presents a difficult paradox concerning position of immobilization. When possible, we have treated such injuries as



FIGURE 1. Fractures of the Base of the Third Metacarpal and the Waist of the Scaphoid, with a Comminuted Colles Fracture of the Joint.

though they were uncomplicated scaphoid fractures, when that could not be done, we have used volar and ulnar flexion of the wrist with inclusion of the proximal phalanx of the thumb in the cast to prevent motion of the scaphoid fragments. The position was changed to cockup in four weeks when there was no danger of displacing the radial fragments.

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pole) of the scaphoid, 2 had fractures of the triquetrum, and there were 1 each of the lunate, capitate and greater multangular.

The combination of radial and scaphoid fractures occurred over a wide age range. The youngest patient was fifteen, and the oldest, seventy-nine. The average age was forty-four and seven-tenths years. More than half the cases were in males. Ten of the 15 patients had radial fractures of the Colles type. 1 was impacted without displacement, 5 had backward tilting of the distal fragment, and 4 had comminuted "T" fractures involving the joint. Of the remaining 5, 3 had a chauffeur fracture of the radial styloid, 1 had a Barton fracture of the dorsal articulating surface, and there was 1 epiphyseal fracture with wide displacement of the distal epiphysis and a dorsal metaphyseal fragment. All these cases resulted from a fall on the outstretched hand except for the fractures of the radial styloid, which occurred from blows forcing the hand into dorsal and radial flexion. One case, similar to that of Cleveland,⁶ had associated fractures of the greater multangular, the scaphoid and the radius (Colles type). Another case (Fig 1) illustrates a different line of force, with fractures of the base of the third metacarpal, the waist of the scaphoid and a comminuted Colles fracture involving the joint. This case required four and a half months of immobilization for bony union to occur in the scaphoid.

DIAGNOSTIC PROBLEM

It is hard enough to diagnose a fracture of the scaphoid when the radius is not broken. A case with separation of the scaphoid fragments presents no diagnostic difficulty, but the barely visible hairline, which may not develop until many days after injury, is a more serious problem. The pain and swelling of the radial fracture mask the signs and symptoms referable to the scaphoid, and the surgeon is apt to see at a glance the gross deformity of the radius without bothering to look farther for a suspicious hairline in the scaphoid. It is very easy to concentrate attention on the radius to the exclusion of the carpus in check x-ray films, in which oblique views are seldom required. A policy of taking frequent careful scaphoid series is the only program that can prevent most errors.^{2, 6, 8}

THERAPEUTIC PROBLEM

None of the authors who discuss the occurrence of fractures of the scaphoid complicated by a comminuted Colles fracture mention the paradox of

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†Surgeon in-chief, Orthopedic Service, Boston City Hospital.

cipitated pertussis organisms used was only 20-000 000 000, these results are impressive even by the most conservative standard

Immunization of Young Infants

It has long been recognized that young infants have little or no inherited immunity to pertussis and that most deaths and complications occur in this age group. Over 50 per cent of all (pertussis) deaths occurred under six months of age and over 75 per cent died before reaching the age of one year.¹³ It was formerly believed that infants under six months did not respond effectively to pertussis immunization, this may well have been true of earlier and less effective vaccines. At all events numerous recent reports have testified to the contrary. Sako¹⁴ following up his earlier studies in this field reports agglutinin responses in 8690 Negro children immunized at ages ranging from two weeks to five years. No significant differences in antibody response of children immunized at different ages were found. Four hundred and ninety-three children immunized before three months of age were known to have been exposed to pertussis within the household, and were compared to 438 exposed controls of comparable age. Pertussis occurred in 13.2 per cent of the vaccinated children and 89.7 per cent of the controls. Incidentally the pertussis attack rate in the former was in general inversely correlated with their agglutinin titers — apparently the first strong evidence that agglutinin titers and protection against clinical pertussis are correlated. Sauer¹⁵ Adams¹⁶ di Sant' Agnese^{91 157 158} and Halpern¹⁵⁹ among others, have also reported successful immunization of young infants, as judged by antibody titers or skin tests. Both Sauer and Sako emphasize the superior agglutinin titers produced by alum-precipitated vaccine as compared to fluid vaccine.

Most investigators have agreed with Sauer¹⁶⁰ in finding a poorer antibody response in early infancy than in late infancy and childhood only. Sako¹⁵⁴ reporting no evidence of such differences. To guard against early relapse of immunity in young infants given pertussis vaccine many workers have stressed the importance of giving a booster dose of pertussis vaccine a year or so later. Confirmation of the efficacy of such a booster dose is presented by Sako,¹⁵⁴ by di Sant' Agnese^{91 158} and by Kendrick and her associates,¹⁹¹ who found ample antibody responses to such injections, the response in di Sant' Agnese's series, however being definitely better in infants first immunized at six to twelve months.

Preparation and Testing of Vaccine

Obviously, even the best results reported with pertussis vaccine are not wholly satisfactory. The principal difficulty at present lies in insufficient

knowledge regarding the antigenic factors responsible for producing immunity to the disease. Recent advances in the purification of the endotoxin¹⁹² and the soluble antigens¹⁹³ of the pertussis bacillus may furnish a basis for more exact knowledge in this respect. Meanwhile, experiments with cruder preparations or whole organisms have contributed much fundamental knowledge. Proom¹⁹⁴ has shown that studies of experimental infection may give different answers depending on the technic employed — for example, intraperitoneal injection of live pertussis organisms in a mouse produces chiefly a toxemia combated successfully by antitoxin whereas intranasal infection is best counteracted by antibacterial antibody. Evans¹⁹⁵ long experienced in the study of pertussis toxin has recently added to the accumulation of evidence that antitoxic antibodies are apparently not of material significance in human infection or immunity and Verwey and Thiele¹⁹⁶ have added to the parallel evidence in animals. Gray¹⁹⁷ in animal experiments has reaffirmed the importance of young virulent cultures in the preparation of potent immunizing agents and his more recent observations suggest that much is yet to be learned regarding the ideal conditions for production of vaccine.¹⁹⁸ A new and somewhat obscure factor has been added with the finding that both virulence and antigenicity of pertussis bacilli are closely related to a hitherto unrecognized property — the ability of pertussis cultures to agglutinate avian or mammalian red cells.¹⁹⁹ If this can be adequately confirmed it may provide an extremely useful tool for further evaluation of stock cultures for vaccine production for screening of vaccine batches for potency and perhaps for confirmation of the clinical diagnosis of pertussis. The procedure is as simple as the Hirst test to which it is analogous from a technical viewpoint.

Potency evaluation of pertussis vaccines by a laboratory technic has long been beset by difficulties in reproducing a clear-cut disease in animals as a challenge of experimental immunization. Kendrick and her associates²⁰⁰ have carried out an extensive study, in collaboration with numerous other laboratories using the intracerebral route for injection of the challenge organisms in mice, their results indicate marked differences between different batches of vaccine. However the highly artificial character of the intracerebral route in contrast to the nasal route for example leaves room for dispute concerning which is the most useful in performing a potency test. The nasal route has long been known and is widely employed^{191 197}, to date it has shown the disadvantage of giving highly variable results. When the inherent difficulties in evaluating the potency of pertussis vaccine can be resolved and laboratory and field trials have been extensively correlated, it will be possible to make more rapid advances in preparation of the vaccine or of its active fractions.

MEDICAL PROGRESS

ACTIVE IMMUNIZATION (Continued)

GEOFFREY EDSALL, M D *

BOSTON

PERTUSSIS

Results Obtained with Vaccine

Opinion regarding the efficacy of pertussis vaccine is still far from unanimous. Bell,⁶ in a recent review of the subject, stated that "health officers have sufficient evidence to permit the use of [pertussis vaccine]" Lewis¹⁷⁴ sums up the conservative view, more widely held in England, that there is still a need for large-scale field trials, and that until these have been carried out no widespread campaign for whooping-cough inoculation in that country is justified. Parish¹⁷⁵ similarly expresses the belief that the laboratory and clinical evidence to date do not prove the effectiveness of specific immunization against whooping cough. Both workers have doubtless been considerably impressed by the flatly negative results obtained in the first extensive controlled study of the vaccine in England, reported three years ago.¹⁷⁶ This point of view was strongly expressed in a critical editorial, concurrent with the English report, which pointed out defects in many of the best known American studies of the vaccine—differences in family size or in time of observation of vaccinated and control groups, lack of any genuine controls and so forth.¹⁷⁷ It is true that some reports of apparently favorable results from pertussis vaccination do not stand up well to critical examination. As an example, one may cite the 436 immunized Winnipeg children observed by Brereton¹⁷⁸ in whom no whooping cough occurred in two and a half years, despite the occurrence of 1171 cases in the city during this period. Such findings suggest—but in no sense prove—that the vaccine used was effective. One may calculate that there should have been about 17 cases among his patients in this period if the vaccine had been ineffective—and if his patients were a representative sample of the child population. No evidence is presented, however, that his patients were not unduly shielded from infection (for example, that they had few or no siblings and limited contacts with other children) or were otherwise not representative of the community as a whole. More convincing, although likewise lacking in controls, is the experience of Tucker,¹⁷⁹ who has seen only 70 cases of pertussis among 5590 children immunized during the last thirteen years. A situation more subject to statistical evaluation is reported by Rodman, Bradford

and Berry,¹⁸⁰ who observed a public-school outbreak, in which the incidence of pertussis was twice as high in the unvaccinated as in those who had received any pertussis vaccine, and almost six times as high as it was in those whose immunization had included at least 50,000,000,000 organisms. However, since the entire outbreak included only 57 cases, the results must be accepted with some reservations. During another outbreak, reported by Lapointe,¹⁸¹ in a foundling home in Quebec, 82 per cent of 550 unimmunized children and infants contracted pertussis, with 5 deaths, whereas no more than 10 per cent of the 100 vaccinated children developed the disease. Despite the lack of a clear-cut basis for comparison between the controls and the children vaccinated, this report is hard to explain except on the assumption that vaccination was highly effective.

Bell⁸² has recently reported a study that approaches the epidemiologist's ideal for evaluation of an immunization procedure. A diphtheria-immunization campaign for infants aged two to twenty-three months was conducted through a group of clinics in Norfolk, Virginia, with the co-operation of the local health authorities. Doctors and nurses were furnished alum-precipitated toxoids for the program, with instructions to administer certain lots if the baby was born in an "odd" month (such as January, March or May) and other specified lots if the birth had been in an "even" month. Neither the parents nor the local health authorities were informed that one set of lots also contained pertussis vaccine. The physician in charge of the study, who saw most of the cases of whooping cough reported by visiting nurses in the immunized children, did not himself know which lots had contained pertussis vaccine. In this fashion it was possible to ensure absolute impartiality on the part of the examining physicians and others engaged in collecting field observations. Statistical analysis showed that both groups were essentially identical in sex, age distribution, color, order in family, age at first inoculation, incidence of other common contagious diseases, and numerous other factors that might have biased the results of the study. These results showed an over-all incidence of pertussis in the controls, which was 3.45 times that in the patients receiving pertussis vaccine. If only frank severe pertussis was counted, the incidence was 8 times as great in the controls as in the vaccinated. In view of the fact that the total dose of alum-pre-

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Immunization with Specific Polysaccharides

As the number of recognized types of pneumococcus increased, and it became established that each was immunologically distinct, the possibility of effective human immunization against pneumococcal pneumonia was generally laid aside, and efforts were directed toward its treatment by physiologic and serologic means. However, the chemical studies of Dochez, Avery and Heidelberger^{216 217} made available in purified form the specific soluble capsular polysaccharides that characterized several of the common types of pneumococcus. Francis and Tillett²¹⁸ showed that intracutaneous injection of these preparations into patients with pneumonia gave rise to antibody formation, this was confirmed, in normal as well as sick persons, by Finland and Sutliff²¹⁹. Earlier disagreement regarding the antigenicity of such preparations in mice—the customary test animal²²⁰—was shown to be due to the existence of two forms of the antigen: the natural acetylated form, and a deacetylated form resulting from treatment with alkali.²²¹ Both were found to be antigenic in man, but only the former induced antibodies in mice.²²²

Felton^{223 224} carried out extensive laboratory-controlled studies on the use of specific polysaccharides of pneumococcus in man. He demonstrated that significant antibody responses could be induced by doses of polysaccharide that were reasonably well tolerated by the recipients. His work formed the basis for collaboration with Army Medical Corps personnel, in a study of immunization against Types 1 and 2 pneumonia in about 70,000 males, mostly under twenty years of age, in New England and the far West.²²⁵ The incidence ratio of Types 1 and 2 pneumonia in 14,000 controls as against 10,700 persons vaccinated in New England was about 1.7:1, but in the much larger western groups (26,000 control and 18,000 vaccinated subjects) the relative incidence was 9:1. However, because of the short season of observation, the lack of strict alternation in selecting the controls, and other factors, these impressive results must be taken with some reservations.

Similar studies on a smaller scale, carried out in several localities over the past decade, have given varying results, which either were not numerically significant or might readily have resulted from natural fluctuations in the incidence of pneumonia. However, there have recently been reported two series of studies in which the results obtained appear to be significant. MacLeod and his associates²²⁶ immunized 8586 soldiers at a technical school, with 0.03 to 0.06 mg. each of Types 1, 2, 5 and 7 polysaccharides, 8449 controls being injected with phenolized saline solution. Age distribution, duration of service and so forth were closely comparable in both groups. The high incidence of pneumonia at this school in two preceding years favored such

an immunization study. Laboratory studies, both on the Army group and on civilian volunteers, had shown, moreover, that such inoculation was followed in almost all cases by striking increases in the specific precipitating antibody titer in the subjects' serum.^{227 228} The incidence of the four types in question, during an average stay of twenty-four weeks per man, was $\frac{1}{4}$ cases in the vaccinated, and 56 in the controls. Furthermore, the carrier rate dropped significantly in the vaccinated group, this drop no doubt contributing to the apparent decrease in the number of cases of Types 1, 2, 5 and 7 in the controls, which was only 17 per cent of the expected rate based on the incidence of higher types not affected by the study. Taking the bacteriologic and epidemiologic data as a whole, the effect of polysaccharide immunization in this group appears to have been striking.

Kaufman²²⁹ has recently reported a six-year study of immunization in elderly persons with Types 1, 2 and 3 polysaccharides. A group of 5750 immunized subjects contracted 3 cases of Type 1, 2 or 3 pneumonia (and 31 cases of other types of pneumococcal pneumonia) during this period, whereas 5153 controls experienced 96 cases of pneumococcal pneumonia, of which 33 were Types 1, 2 and 3.

Serum titrations before and twenty-one days after immunization showed increases of several hundred times in antibody content after injection of the antigens. Local reactions occurred in 5 per cent, and general reactions in 2 per cent of the subjects. In patients who developed pneumonia, the duration of illness and the severity of toxemia were less in the immunized than in the controls. Total person-years of observation are not given, nor is the method of selection of controls stated, the peculiarly higher incidence of "higher types" of pneumonia among the controls is not explained.

Nevertheless, the sum total of all available observations cited above strongly indicates that immunization with pneumococcal type-specific polysaccharides exerts a strong protective effect in man against the homologous types of pneumonia. Such polysaccharide preparations have recently been put on the market, in two forms: a mixture of Types 1, 2, 3, 5, 7 and 8, primarily for use in adults and adolescent children, and a mixture of Types 1, 4, 6, 14, 18 and 19, for protection of infants and young children against the types to which this age group is most subject. Both these multiple-antigen preparations have been shown to be effective in stimulating antibody production.²³⁰ The Massachusetts Department of Public Health has recently called attention to the value of such immunization, recommending that it be considered in the elderly, the very young, special occupational groups with high natural incidence of pneumococcal pneumonia and patients about to undergo major surgical operations.²³¹ If immunization is employed for this latter category, however, it should be borne in mind

Meanwhile, the possibility has arisen that pertussis vaccines — like typhoid vaccines — will have to be prepared in polyvalent form. Wilson and Miles²⁰¹ have noted that it may ultimately prove necessary to include the parapertussis organism in pertussis vaccines. With such a thought in mind, Rambar, Howell and Denenholz²⁰² have prepared a combined pertussis-parapertussis vaccine that produced clear-cut opsonic antibody rises against both components and actually appeared to induce a better response against the pertussis bacillus than that obtained with the monovalent pertussis vaccine.

Reactions

Since the start of extensive whooping-cough immunization, reactions to the injection of the vaccines used have been sufficiently frequent to cause occasional concern. Local tenderness and swelling have been ascribed to the use of too concentrated a suspension, or to the irritating effects of alum precipitates. Lapin²⁰³ found that variations in concentration of organisms from 15,000,000,000 to 40,000,000,000 per cubic centimeter caused no significant difference in incidence of local or general reactions. He believes that the irritating effects of alum are due chiefly to its low pH. Sterile abscesses (or "antigenic cysts"), which may occur in as many as 2 or 3 per cent of cases, are usually associated with alum-precipitated preparations. Tucker¹⁷⁹ and Sauer¹⁸⁵ stress the importance of injecting distally, and carefully wiping free alum off the needle tip before injection, to avoid alum abscesses. Sako¹⁸⁴ employed these precautions as well as the recommendation of Bell¹⁶² that deep subcutaneous injection be employed, and he added the precaution of taking especial care to avoid intracutaneous injection. Following these precautions, he observed 1.5 per cent "alum abscesses" in 2021 inoculations. On the other hand, other reactions were more than twice as frequent with fluid vaccine as with alum-precipitated material.

A matter of more serious concern is the occasional occurrence of convulsions or, more rarely, of a frank encephalopathic syndrome following pertussis vaccination. Sako²⁰⁴ noted 2 cases of vomiting, diarrhea and convulsions in his earlier series, and several similar reports have been cited by Byers and Moll,²⁰⁵ including 4 fatal cases. Brody and Sorley²⁰⁶ reported the case of a ten-month-old infant who exhibited generalized hypotonia, somnolence and difficulty in micturition following each of three doses of pertussis vaccine. At the age of forty-three months he received a skin test with pertussis vaccine, after which a generalized flaccid paralysis developed, the patient dying of bronchopneumonia seven weeks later. Byers and Moll²⁰⁵ have collected 15 cases of convulsions following pertussis-vaccine inoculation, which were seen at the Boston Children's Hospital over a ten-year period. Thirteen exhibited residual damage when last seen. It is difficult to

evaluate such findings, since many other causes of encephalopathy exist, and the association with pertussis vaccination might conceivably be one of coincidence. The absence of comparable reports from other communities may be reassuring, but this cannot be evaluated until others have searched for this syndrome as extensively as Byers has done. Approximately 40 cases of possibly similar nature have been disclosed through individual case reports²⁰⁷ and an extensive questionnaire sent to some 55 physicians whose collective experience covers at least several hundred thousand injections.²⁰⁸ The net impression gained from this survey is that such reactions may occur, but that they are exceedingly rare. Meanwhile, the National Institute of Health has during the two years developed a toxicity test for pertussis vaccines. The application of this test may serve to eliminate excessively toxic batches of vaccine, which may have been responsible for reactions of the type described.

PNEUMOCOCCAL PNEUMONIA

Immunization with Bacterial Suspensions

The capacity of extracts from cultures of pneumococcus to furnish protection against pneumococcal infection in animals was demonstrated over fifty years ago.²⁰⁹ An understanding of the immunologic and chemical properties of the specific soluble substance of the pneumococcus did not come about until much later, however, hence early attempts to immunize human beings against lobar pneumonia were carried out with the use of whole bacterial vaccines. The most widely cited of these studies^{210, 211} yielded promising results. Cecil and Austin,²¹⁰ for example, in a study at Camp Upton, inoculated 12,519 "stable" troops with a vaccine composed of Types 1, 2 and 3 organisms, using about 20,000 other troops (of which perhaps 75 per cent were "stable") as controls. The incidence of Types 1, 2 and 3 pneumonia, over a period of ten weeks, was nil in the vaccinated and 18 in the comparable stable control group. However, since the incidence of other types of pneumonia — particularly those due to the streptococcus — was likewise greater in the controls than in the vaccinated, the validity of this experiment is open to question. The South African studies of Lister and his colleagues^{211, 214} cover longer periods and larger groups, among native laborers in the goldfields. However, no actual controls to these groups were set up, so that the results from vaccination had to be evaluated by comparison with the incidence of pneumonia in unvaccinated mine groups, or in years prior to vaccination. Although the results strongly suggested that vaccination was materially effective in some cases at least, there are alternative explanations for the figures observed, and there are some figures showing less promising results.²¹⁵ Hence this series of studies must also tentatively be regarded as inconclusive.

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Similar studies on a smaller scale, carried out in several localities over the past decade, have given varying results, which either were not numerically significant or might readily have resulted from natural fluctuations in the incidence of pneumonia. However, there have recently been reported two series of studies in which the results obtained appear to be significant. MacLeod and his associates²⁶ immunized 8586 soldiers at a technical school, with 0.03 to 0.06 mg. each of Types 1, 2, 5 and 7 polysaccharides, 8449 controls being injected with phenolized saline solution. Age distribution, duration of service and so forth were closely comparable in both groups. The high incidence of pneumonia at this school in two preceding years favored such

an immunization study. Laboratory studies, both on the Army group and on civilian volunteers, had shown, moreover, that such inoculation was followed in almost all cases by striking increases in the specific precipitating antibody titer in the subjects' serum.^{27, 28} The incidence of the four types in question, during an average stay of twenty-four weeks per man, was $\frac{1}{4}$ cases in the vaccinated, and 56 in the controls. Furthermore, the carrier rate dropped significantly in the vaccinated group, this drop no doubt contributing to the apparent decrease in the number of cases of Types 1, 2, 5 and 7 in the controls, which was only 17 per cent of the expected rate based on the incidence of higher types not affected by the study. Taking the bacteriologic and epidemiologic data as a whole, the effect of polysaccharide immunization in this group appears to have been striking.

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that such immunity as may develop cannot be expected to appear for at least nine days, and will probably not be adequate in less than two weeks after inoculation. Also, it is imperative to re-emphasize the fact that immunity induced by pneumococcal polysaccharides is effective only against the homologous types of pneumococcus, except where a low degree of cross immunity against related types may be induced.

RABIES

Present Situation, Dog Vaccination

Although rabies has been on the wane in certain areas, notably New England, it has been definitely on the increase elsewhere in the United States during the last few years. This trend is clearly set forth in a recent review by Johnson,²³² who summarizes the epidemiology, etiology, laboratory characteristics, symptoms in animals, diagnostic features and preventive measures applicable to the disease, in a presentation distinguished for its clarity and readability. The review calls attention to the marked increase in animal rabies in recent years over the United States as a whole, the number of reported rabid animals throughout the country was higher in 1944 than in any previous year on record. In fact, the spread of this disease among animals in New York, Pennsylvania, Maryland, Virginia and other states in the last few years has led to several studies and conferences from which have come broadly conceived, long-range programs for control of the disease on a nationwide basis.²³³⁻²³¹ Such control is needed not only because of the risk to human life engendered by the disease, and the discomfort, inconvenience, expense and actual danger incurred by persons receiving the vaccine, but also because of the considerable loss in farm stock caused by rabies: there were 2800 reported deaths from this disease among cattle alone during the period 1938-1945 inclusive, the actual number being unquestionably much higher.

Johnson's review, the New York Academy of Medicine Report, and the April 1947 conference headed by Dr. R. A. Kelser, all agree on the following recommendations:

Rabies control can only be accomplished effectively through federal participation and co-ordination — the agencies most obviously concerned being the United States Public Health Service, the Bureau of Animal Industry and the United States Fish and Wildlife Service.

Reporting of animal rabies should be universally required.

Dog licensing should be enforced, stray dogs should be impounded, and dog quarantine should be applied, especially in areas where animal rabies is present.

Dog vaccination should be encouraged on the widest possible scale, and at little or no cost

to the dog owner (since few owners will avail themselves of the service otherwise). In urban areas, dog licenses should be made contingent upon vaccination.

A widespread and generalized public-education program should be undertaken, particularly to acquaint the public with the need for control of rabies, the advantages of rabies control to dogs as well as man, and the now proved value of dog vaccination. Johnson²³² remarks upon the still persistent belief that dog vaccination is ineffective — a belief based upon the poorly conceived experiments and low-potency vaccine of some years ago. The effectiveness of a potent vaccine, properly used, is shown in an experiment of his, referred to elsewhere²³³, 52 vaccinated dogs, along with 52 unvaccinated dogs, were injected with street virus one year after vaccination. Death occurred in 11.5 per cent of the vaccinated as against 79 per cent of the control animals. Such experiments as these and other experimental and field studies previously cited¹¹ have established the efficacy of dog vaccination. Its practical value has also been recently affirmed in New York State, in ten counties having 78 per cent of the enumerated dogs vaccinated, the incidence of rabies in unvaccinated dogs was fifteen and eight-tenths times that in the vaccinated animals.²³⁵ The value of protection of one's pets is also illustrated in the saga of a rabid dog that recently roamed through three townships before it was killed, and bit 13 unvaccinated dogs in succession — several of which had to be destroyed as a result.²³¹ Effective control of rabies, however, cannot be achieved merely through local or even statewide programs, since rabid animals do not recognize state boundaries. Hence the recommendation^{232, 231} for federal rabies-control legislation is especially pertinent at this time of increasing prevalence of the disease in animals.

Methods of Preparing Rabies Vaccine

The factors that may influence the potency of rabies vaccine continue to be under scrutiny. Habel²³⁷ compared the potency of vaccines inactivated by ultraviolet irradiation, by phenol and by chloroform, and found the ultraviolet-treated material to be greatly superior. A new method of inactivation, employing nitrogen mustards, has been applied experimentally,²³⁸ but has not yet had extensive trial in either animals or man.

The choice of virus strain for preparation of vaccine may still be open to question, since Habel and Wright²³⁹ found marked differences in immunizing potency of six different strains in routine use. Their paper gives a detailed description of what is now the standard method for testing the potency of rabies vaccine. The standard of potency set under this method is considerably higher than the average level that prevailed before the method was pro-

nulgated so that the vaccines now obtainable may be used with far greater assurance of efficacy than before

Although greatly improved in potency the currently available vaccines contain large amounts of impurities in the form of brain-tissue constituents. Because of the numerous recent studies noted below, which indicate that brain-tissue injections may induce severe damage to the nervous system present interest is focused on the problem of purifying the vaccine. Two recent reports^{240 241} have described methods for removing most or all of the lipid constituents of the vaccine, by extraction with organic solvents at low temperatures. The resulting preparation appears to be actually more potent than the crude material²⁴⁰

Reactions Following Antirabic Vaccination

Paralytic accidents following administration of rabies vaccine have been found to occur about once in 5800 cases, with death resulting in about 1 out of each 23,000 cases treated²⁴². The incidence fluctuates greatly, however, after more than a decade during which no fatal cases were noted in Massachusetts, 2 deaths occurred in 1947²⁴³. A high incidence of such accidents has also been recently noted elsewhere^{244 245}. Irrespective of whether such accidents are sporadic or represent a definite upward trend, the 2 recent deaths in this state have served as a reminder that the use of rabies vaccine must be considered in the light of the total situation. In Massachusetts, for example, endemic animal rabies has not been present for four or five years. Here rabies vaccine can wisely be withheld except in cases of proved exposure to the disease, or in persons bitten in the Berkshire area, which is subject to reinfection at any time by rabid animals from the neighboring endemic foci in New York State. The advisability of such a conservative review of the problem has been stressed by the Massachusetts Department of Public Health²⁴³ and in an accompanying editorial in the *Journal*²⁴⁶. Sellers,²⁴⁷ whose experience has been gained in one of the most heavily rabies-infected areas in this country, shares the view that antirabic vaccination is not to be lightly undertaken, stating his belief that "it has caused more deaths than has rabies when given to persons only indirectly or remotely exposed". He notes that in the 7 cases of treatment paralysis that he has followed, 4 patients died, only 2 of these 7 were in persons bitten by rabid dogs the other 5 (including 3 of the deaths) occurring in persons only remotely exposed to rabies.

For a number of years it has been suspected that encephalitis following rabies vaccination might be the consequence of an iso-allergic reaction resulting from injection of brain substance, which is organ-specific rather than species-specific. Some years ago Rivers and his associates^{248 249} succeeded in producing lesions in the nervous system of

monkeys by repeated injections of suspensions and alcoholic extracts of rabbit brain. Recently, Morgan²⁵⁰ and Kabat, Wolf and Bezer²⁵¹ have produced encephalomyelitis in monkeys by a few injections of brain substance combined with tubercle bacilli paraffin oil and an emulsifying agent, according to the technic developed by Freund¹⁴⁸. Using guinea pigs Freund et al²⁵² produced meningo-encephalitis and paralysis of the hind legs with only one injection of such an emulsion of brain tissue. Furthermore some of the animals surviving the first injection developed acutely fatal reactions after reinjection of the same material three or four weeks later. Kopeloff and Kopeloff²⁵³ confirmed these findings in guinea pigs, and produced paralysis by similar means in rabbits. Recently, Jungblut²⁴ has added further confirmatory evidence of the sensitizing capacity of brain substance. Thus, there are ample experimental data to indicate that repeated injections of brain substance can, under certain as yet obscure conditions, induce an iso-allergic reaction that may result in varying degrees of destruction of the gray and white matter of the brain or spinal cord. It is, of course, yet to be proved that human paralytic accidents are caused by such a reaction, but the available evidence points in this direction. Still to be explained however, is the relative rarity of such reactions.

The experiments cited provide a basis for attempting to define the specific substance or substances in brain tissue that are responsible for these reactions, and to develop physical or chemical methods for their removal. Recent purification studies^{240 241} may lead to such findings, but this has as yet to be determined. A different approach to the solution of this problem is suggested by Chen-Jen and Zia,²⁵⁵ who have prepared a potent vaccine from rabies-infected brains of guinea-pig fetuses, fetal brain tissue having been found by Zia²⁵⁶ and others²⁵⁷ to be apparently nonantigenic. Meanwhile, this and other aspects of the problem are now under active investigation in several laboratories, and it is to be hoped that these studies will be fruitful.

SMALLPOX

Recent Occurrence of Virulent Smallpox in the United States

On the whole, the incidence of smallpox has continued to decline in the continental United States during the last few years. This decline has recently been the subject of an editorial comment²⁵⁷ which cited Dr. Benjamin White's²⁵⁸ reminder of over twenty years ago, that smallpox is never conquered but "is at best only held at bay by the continued practice of vaccination". Recent experience in the Orient, on the West Coast of this country and later in New York City has amply confirmed this already well established fact. The severity of smallpox as seen in the Orient, as well as the frequency

of its occurrence in presumably vaccinated persons, was vividly described a year ago by Agerty,²⁶⁹ who observed 17 cases with 10 deaths among American personnel in Japan. Only 4 of these patients had histories or scars indicating that they had been vaccinated in childhood. All but 3 had been recorded as having been vaccinated within the preceding two years, in 2 vaccinoid reactions had developed, the other 12 being noted as "immune," "doubtful" or "unsuccessful" (The probable significance of "immune" reactions is discussed below.) Reports from other sources have indicated scattered failures to protect American personnel in the Orient by the use of the standard vaccination procedure and the vaccine available at the time. Hence it was not surprising that cases appeared among servicemen returning to the West Coast. Such cases caused a small outbreak in San Francisco early in 1946,²⁶⁰ and a much larger one in and around Seattle.^{261, 262} The latter outbreak produced at least 65 cases with 20 deaths (a 30.8 per cent case mortality) and took four months to stamp out. An incidental result of this outbreak was an unprecedentedly successful vaccination campaign in neighboring British Columbia, which probably reached 250,000 people. This may be contrasted with the 80,000 in the province who submitted to vaccination fourteen years earlier in the presence of an actual smallpox outbreak. Apparently, the public at large has become widely educated, in the interval, regarding the wisdom of being vaccinated.²⁶³

If proof of this acceptance of vaccination were needed, the New York City outbreak of March-April 1947 has furnished it. A total of 8 confirmed cases in New York City, and 4 outside the city, occurred over a period of about six weeks. The findings in most of these cases have been thoroughly expounded and discussed in a clinicopathological conference.²⁶⁴ The first case was atypical and not recognized until secondary cases were diagnosed, by which time it was evident that numerous scattered tertiary cases might be expected to appear. The decision was therefore made to vaccinate the entire city. Over 6,000,000 people were actually vaccinated during the following two weeks.²⁶⁵ This was accomplished by extraordinary efforts on the part of local medical and health personnel and also of the producing firms, which were faced with a demand for vaccine unparalleled both in size and in urgency. This outbreak caused widespread alarm elsewhere, increases in vaccination demands being observed at least as far away as Michigan. Although states such as Massachusetts and Michigan, having their own production facilities, were able — with difficulty — to keep pace with the demand, many other communities saw their supplies of vaccine temporarily exhausted. The experiences of the last two years suggest that it is entirely possible for several virulent foci of smallpox to be established in this country at about the same time. In

such an event, vaccine supplies would certainly be temporarily inadequate. This possibility focuses attention on the importance of maintaining an immune population, by vaccination in infancy and periodic revaccination.²⁶⁶ This is clearly demonstrated by the New York experience, which showed that perhaps 50 per cent of the people in that urban area were susceptible to infection, as indicated by either a primary or a vaccinoid reaction.⁶

England has had similar but considerably more numerous experiences, as indicated in several excellent reports of outbreaks of virulent smallpox in that country.²⁶⁷⁻²⁷² Mortality rates have been high — for example, 3 deaths in 11 cases,²⁶⁸ 9 in 31 cases,²⁶⁹ and 6 in 30 cases.²⁷¹ Control has been difficult owing to unfamiliarity of local physicians with the diagnosis, to the high level of susceptibility in England, where compulsory vaccination has always been resisted and in fact has recently been abandoned²⁷³, and to the marked and prolonged contagiousness of infected materials, smallpox crusts sometimes remaining infectious for as long as a year.²⁷⁴

Interpretation of Vaccination Reactions

The extensive need for mass vaccination during and after World War II and the many opportunities for contracting smallpox confronting persons hitherto safe from the disease have led to an extensive and critical re-evaluation of the phenomenon of vaccination. The official requirement of a vaccination certificate, imposed on an unprecedented number of travelers, gave rise to various problems outstanding among which was the question of how to interpret an "unsuccessful vaccination," especially in persons who failed to develop a "take" after repeated attempts. For example, Broom²⁷⁵ reports the experience resulting from vaccinating 1221 UNRRA personnel, 238 of whom did not "take." On revaccination of 201 of this group, 80 per cent were again negative. Broom suggests that such persons are "insusceptible" to vaccination, and that allowance should be made for such a classification on vaccination certificates. He is supported in this by Mitman,²⁷⁶ MacKenzie,²⁷⁷ Stuart²⁷⁸ and indirectly, also by Cavaillon,²⁷⁹ who suggests that it may be desirable to indicate, "in unsuccessful cases, that vaccination had been carried out twice or several times, at certain intervals." In fact, some observers have regarded "no reaction" as synonymous with immunity,²⁸⁰ but such views run into direct conflict with the prevailing belief, at least in this country,²⁸¹ which holds that unsuccessful vaccination is never to be accepted as final and merely calls for another attempt. However, it must be recognized that such a doctrine can be incompatible with the realities of human activity, as the medical officer of the Port of London has cogently pointed out²⁸², for example, a traveler cannot ordinarily

postpone a sailing date until a long series of attempts at revaccination is at last successful

A significant portion of the difficulty in obtaining satisfactory "takes" appears to derive from ineffective technic of vaccination. Several recent English communications have called attention to the deficiencies of the scratch technic which has been generally used in that country. Mole,²⁵³ performing alternate scratch and multiple-pressure vaccinations, obtained 83 per cent "takes" by the scratch method as against 94 per cent by the multiple-pressure technic. Vaughan²⁵⁴ and Lovett²⁵⁵ similarly report repeated successes in multiple-pressure vaccination, in persons previously scratched unsuccessfully by the older technic. Within the past year the use of the multiple-pressure method (which Parish²⁵⁶ and others in England have advocated for several years) has been officially recommended by the British Ministry of Health²⁵⁷ and by an expert committee of WHO on International Epidemic Control.²⁵⁸ It will be of interest to observe whether the problem of "insusceptibility" is diminished in the future as a result of this trend. In justice to the scratch technic, however, it should be noted that on occasion almost complete success has been achieved by its use. When smallpox appeared on a troopship bound for New Zealand, 94 per cent of the 1648 men on board were successfully vaccinated by the scratch method on the first attempt.²⁵⁹

A subtler problem arises from the interpretation of the so-called "immune reaction"—the raised papule that reaches its height on the second or third day and then subsides without vesicle formation. This reaction is very widely accepted as adequate evidence of immunity. Doraisingham,²⁶⁰ for example, notes that smallpox in Singapore has been extremely rare for thirty years, in a population of which 73 per cent (in a large sample) gave an "immune" reaction to vaccination, he regards this as strong evidence that such a reaction represents genuine immunity. But it has been known for many years that heated, inactivated vaccine virus can produce a papular reaction indistinguishable from that caused by live virus. This was well shown by Andervont and Rosenau,²⁶¹ and by MacKinnon and Defries²⁶² among many others, and has been recently confirmed.^{275 293 294} Benenson²⁹⁴ has carried this farther, showing that heated and unheated vaccine from the same batch can even produce identical vesicular reactions. Thus, it is not always possible to tell whether the result observed was caused by live or dead virus. Furthermore, he has shown that the production of a papular or vesicular lesion with heated virus is not ordinarily associated with a serologically demonstrable immune response. Using the complement-fixation test and the agglutinin-inhibition technic developed by Nagler,²⁹⁵ Benenson and Kempe²⁹⁶ have demonstrated that an early immune type of reaction produced by live

virus is generally accompanied by a rise in the subject's serum antibody titer, but that no such rise is observed if heated virus is used. Benenson therefore believes—agreeing in this instance with Mitman⁷⁶—that a reaction to vaccination that reaches its height within seventy-two hours is quite literally uninterpretable. If this proves to be the case, an early reaction can no longer be regarded as evidence of successful revaccination, and the vaccinator must depend for success, in such cases, entirely upon proper technic and the assurance of a supply of fresh potent vaccine. Thus it again becomes evident that successful revaccination depends very largely upon observance of the expiration date on each package of vaccine, and also upon the utmost diligence in keeping the vaccine frozen when it is not actually in use or transit.

Little help has been offered by way of varying the route of administration of smallpox vaccine. A recent report from Finland indicates that long-term immunity in 369 cases following subcutaneous vaccination was lower than that produced by scarification.²⁹⁷

Technic of Preparing Vaccine

It is still commonly stated²⁹⁸ that sterile—that is, bacteria-free—smallpox vaccine cannot be produced in calves. Numerous workers have reported the use of penicillin to reduce the bacterial count in such vaccine. Equally striking results can be obtained, however, by the use of a quaternary ammonium detergent, such as "roccal," during incubation of the virus and while the vaccine is being harvested from the animal used.²⁹⁹ The effectiveness of this method has been amply confirmed by Dr J. A. McComb at the Massachusetts Antitoxin and Vaccine Laboratory, where bacteria-free preparations of ample potency have been repeatedly obtained. Many other institutions have assuredly done likewise.

Smallpox vaccine produced in fertile hen's eggs has not received wide acceptance as yet, but it has been in general distribution in Texas for several years. Of 779,250 doses distributed in that state, reports were obtained on 125,892 vaccinations, 87.3 per cent of which gave primary, accelerated or "immune" reactions. In a group of 39 persons vaccinated with chick-embryo vaccine one to five years previously, revaccination with calf vaccine gave 35 immune and 4 accelerated reactions. Thus, the duration of immunity produced by egg vaccine appears to be within normal limits. The egg vaccine was reported to have caused milder local reactions, smaller vesicles, less secondary infection and less systemic disturbance than the standard calf vaccine.³⁰⁰ However, until egg vaccine has been shown to be effective in stopping a smallpox epidemic, it will apparently not be generally accepted by health authorities, since the merits of calf vaccine in this respect are already well established.

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Interpretation of Vaccination Reactions

The extensive need for mass vaccination during and after World War II and the many opportunities for contracting smallpox confronting persons hitherto safe from the disease have led to an extensive and critical re-evaluation of the phenomenon of vaccination. The official requirement of a vaccination certificate, imposed on an unprecedented number of travelers, gave rise to various problems outstanding among which was the question of how to interpret an "unsuccessful vaccination," especially in persons who failed to develop a "take" after repeated attempts. For example, Broom²⁷⁵ reports the experience resulting from vaccinating 122 UNRRA personnel, 238 of whom did not "take." On revaccination of 201 of this group, 80 per cent were again negative. Broom suggests that such persons are "insusceptible" to vaccination, and that allowance should be made for such a classification on vaccination certificates. He is supported in this by Mitman,²⁷⁶ MacKenzie,²⁷⁷ Stuart²⁷⁸ and indirectly, also by Cavillon,²⁷⁹ who suggests that it may be desirable to indicate, "in unsuccessful cases, that vaccination had been carried out twice or several times, at certain intervals." In fact, some observers have regarded "no reaction" as synonymous with immunity,²⁸⁰ but such views run into direct conflict with the prevailing belief, at least in this country,²⁸¹ which holds that unsuccessful vaccination is never to be accepted as final and merely calls for another attempt. However, it must be recognized that such a doctrine can be incompatible with the realities of human activity, as the medical officer of the Port of London has cogently pointed out²⁸², for example, a traveler cannot ordinarily

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Complications

Eczema vaccinatum continues to occur occasionally here³⁰¹ and elsewhere in eczematous children who are permitted, through ignorance or error, to come in contact with recently vaccinated persons. Such patients still occasionally die,²⁹⁸ very much more rarely than before chemotherapeutic agents were available and modern knowledge of the care of such patients was developed. Two deaths were observed among 36 cases arising in conjunction with the mass vaccination of 6,000,000 people in New York City last year.⁶ Excellent descriptions of 16 of these cases, with a review of the pertinent literature, have recently appeared.³⁰² Fifteen other cases in the same outbreak have been described separately.³⁰³

Post-vaccinal encephalitis remains, in this area, a very rare complication. Even cases reported as such are not always correctly diagnosed. Cavaillon et al.³⁰⁴ report that, among over 1,000,000 vaccinations in the Paris area after a recent smallpox outbreak, notifications of 2 cases of "post-vaccinal encephalitis" were given, on post-mortem examination, however, death was found in both to have been due to bronchopneumonia. An analogous instance occurred in Boston a few years ago. In some countries, however, true post-vaccinal encephalitis occurs in sporadic outbursts of puzzling nature and localization. In and around Basel, 6 cases occurred among 30,000 vaccinations in the urban district in 1945, and 9 more occurred in the rural environs, whereas in Berne no cases occurred among 100,000 vaccinations.³⁰⁵ In a very comprehensive summary of reports of this disease from all parts of the world, Stuart³⁰⁶ notes case incidences ranging from 1 per 641 vaccinations (Tyrol, 1929) to none in over 1,000,000 (France, 1923-1928, and Italy, 1927). The evidence is clear that this complication is persistently recurrent in some areas, and virtually nonexistent in others, without relation to the source of the vaccine used, the manner of use or any other known technical factor. All reports agree that the incidence is far less in infants under three years of age than in older subjects^{300, 306}, it appears also to be rarer after revaccination, although 26 cases following revaccination have been observed in Holland.³⁰⁶ The limited experience in treating post-vaccinal encephalitis with convalescent serum — chiefly in England — is equivocal, 8 of 14 treated patients from 1940 to 1945, inclusive, recovered as against 21 recoveries in 44 untreated cases.³⁰⁷ There is a fifty-fifty chance that this difference was accidental.

To the collection of miscellaneous and bizarre reactions to vaccination there has been added a report from England of a high incidence of evanescent photosensitization rashes resulting from the combined effects of sulfanilamide, sunshine and vaccination. Rashes did not appear in persons in

whom vaccination had failed or been refused. The mechanism of the reaction remains unexplained.³⁰⁸

Many thoughtful investigators have considered the possibility that vaccination might cause abortion or fetal malformation in a pregnant woman. During the recent city-wide vaccination program in New York City, Bellows, Hyman and Merritt¹⁴³ observed the effect of vaccination on pregnancy in a series of 720 vaccinated women and 173 controls. No significant differences were demonstrated between the vaccinated and control groups in the incidence of malformation, stillbirth, abortion or infant deaths.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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CASE 35281

PRESENTATION OF CASE

A forty-seven-year-old housewife was admitted to the hospital complaining of abdominal swelling.

Thirteen years before admission, following the birth of normal twins, the patient developed a post-partum psychosis with hallucinations. She was in a mental hospital for about two years, but improvement was incomplete. At home, during the subsequent decade, she remained mentally disturbed, but tended the house. Her appetite was always very poor, and her diet was fair with few eggs and rare fish and meat. Her menses were normal until fifteen months before admission, when amenorrhea and hot flashes appeared. Subse-

quently she felt increasing fatigue, anorexia and weight loss, with intermittent numbness and tingling in her feet. Her physician prescribed vitamins and administered liver injections, without improvement. The symptoms increased in severity during the year before admission. Her legs and hands had occasional episodes of tingling. In the month before admission she noted weakness of her legs on walking and climbed stairs with difficulty. In the few months just before admission she also noted that her legs had a tendency to develop ecchymosis easily on trauma, and she had occasional retching in the morning. For six months before admission, she consumed 5 or 6 ounces of whiskey and a bottle of beer daily in the hope that her appetite would be stimulated. There was no favorable response, however, and she ate about a fourth of a normal food portion. Ten days before admission, she developed watery diarrhea, which cleared up in two days. She felt weak, and one week before admission noted that her abdomen was swelling, and that there was mild ankle edema. She went to bed. Two days later her eyes were yellow, and her urine dark brown. No abnormality in the stools was noted. Abdominal swelling increased in the few days before admission.

She had never been jaundiced before, and had not been exposed to other jaundiced people. There was no history of gall-bladder disease.

Physical examination showed a thin, tremulous, icteric woman with a mousy odor to her breath. Her abdomen was tense and distended, and shifting flank dullness was present. There were no periumbilical dilated veins. The liver was enlarged to midway between the costal margin and umbilicus.

The edge was very firm. The spleen was not palpable.

The blood pressure was 90 systolic, 65 diastolic. The temperature was 99°F, the pulse 100, and the respirations 20.

Examination of the blood showed a white-cell count of 26,000, with 79 per cent neutrophils, 12 per cent lymphocytes, 5 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The hemoglobin was 11 gm. The urine was dark amber, with a specific gravity of 1.013 and gave a +++ test for bile. The stools were soft brown and guaiac negative. The alkaline phosphatase was 21 units, the nonprotein nitrogen 18 mg, the albumin 2.85 gm, and the globulin 2.69 gm per 100 cc. The cholesterol was 180 mg per 100 cc, and the sodium 125.2 milliequiv and the chloride 78 milliequiv per liter. The van den Bergh reaction was 5.6 mg per 100 cc direct and 7.2 mg indirect, and the cephalin-flocculation test was ++ in forty-eight hours. The prothrombin time was 23 seconds (control, 15 seconds).

On x-ray examination the findings in the chest were not unusual, and the findings in the esophagus were suggestive but not diagnostic of varices.

On the second hospital day an abdominal paracentesis yielded 2100 cc of slightly greenish fluid, with a specific gravity of 1.008 and 130 red cells and 20 lymphocytes per cubic millimeter. The patient did poorly. On the third hospital day alimentation with Levine-tube feedings was instituted. She became disoriented, and then unresponsive. The icterus did not increase, but ascites rapidly reaccumulated. The temperature rose to 102°F, and the white-cell count reached 40,000.

The patient's condition continued to deteriorate, and she died on the ninth hospital day.

DIFFERENTIAL DIAGNOSIS

DR C W FAIRLIE: When a woman enters the hospital with a history of ascites and jaundice for one week and dies within nine days, we have to assume that she died from liver disease. The questions are, What kind of liver disease and what precipitated this rapid demise? The first thought that comes to mind with so rapid a fatality is acute yellow atrophy or acute necrosis, but I do not believe that the patient had this condition. I think, rather, that she had a long-standing cirrhosis with some catastrophe superimposed that caused the final decline.

I will review the history in search of clues toward this conclusion. The mental illness I can make nothing of except that it contributed to her having apparently a subnormal diet over a period of ten or more years. The amenorrhea appeared just at the onset of her symptoms, fifteen months before admission. Since it was accompanied by hot flashes, I doubt that it was amenorrhea due to debilitating disease but rather was the menopause

appearing at the age of forty-seven. The symptoms of anorexia, fatigue and weight loss for fifteen months are common in cirrhosis, but they are frequent in other conditions. The tingling and numbness in her legs suggest peripheral neuritis, but this was never confirmed by other evidence. The alcohol intake is not noted until the mention of its use as an appetizer for six months before entry, but one who turns to this amount of appetizer and continues it even though it is not helping has probably enjoyed the medicine before. Diarrhea was noted ten days before admission and did not recur. A mousy odor to the breath is mentioned. Interpretation of this finding is difficult from the printed word or, indeed, from examining the patient. The liver was enlarged to midway between the costal margin and the umbilicus, and the edge was firm. That is an important observation and would be most unlikely in a patient about to die, nine days later, from acute yellow atrophy of the liver.

The white-cell count of 26,000, and later of 40,000, must be a clue to the underlying process, but not a very specific one. It can occur in acute necrosis of the liver. However, it could also occur with infection or with severe hemorrhage. The phosphatase of 21 Bodansky units per 100 cc is higher than that usually seen with parenchymal liver disease but such exceptions are becoming increasingly familiar. Regarding the albumin and the globulin, it is a pleasure to see them stated as such with no reference to the ratio obtained by dividing these two unrelated quantities one into the other. The low albumin is suggestive of long-standing liver disease but could occur with acute hepatitis or acute necrosis also. The sodium of 125 milliequiv per liter, together with the blood pressure of 90 systolic, 50 diastolic, forces one to mention Addison's disease, but there is nothing else to go with it and I think this electrolyte depletion was merely a part of the acute liver failure.

I would like to see the x-ray films particularly to discover whether the line of the right leaf of the diaphragm is smooth and how much evidence there is for esophageal varices.

DR JOSEPH HANELIN: I think the chest is essentially normal. The right side of the diaphragm is not unusual in appearance. The lungs appear clear. The heart is not enlarged. We have a single spot film of the barium-filled esophagus, and there are definitely wide folds, with undulating contours that strongly suggest varices. I do not know whether there are other films that are more suggestive, but this is almost diagnostic of varices.

DR FAIRLIE: That is strong support for the assumption that she had long-standing liver disease rather than only an acute process—an assumption that is strengthened by the initiation of the final episode with jaundice and ascites but without other symptoms, she was not apparently acutely ill in

other respects. That would be unusual for acute yellow atrophy. The liver was large and very firm, which would likewise be unusual. Further support for the presence of long-standing liver disease is found in the fifteen months' history of nonspecific symptoms and the history of poor nutrition, probable alcoholism and probable esophageal varices.

We thus come to the conclusion that she had portal cirrhosis. What, then, caused her sudden decline? One of the common phenomena that cause cirrhotic patients to become decompensated is infection. This can be an infection of any kind. Even a brief episode of gastroenteritis can be responsible. The white-cell count suggests infection in this patient, but there were no localizing signs. I suppose it could have been a hidden infection, such as mediastinitis, or a deep phlebitis. But there is no reason to think of such entities except that we are searching for infection. Under the heading of infection should be mentioned viral hepatitis. It is uncertain how large a part viral infection of the liver plays in the course of chronic liver disease due to other conditions.

Another common incident precipitating hepatic failure in cirrhotic patients is hemorrhage. It is familiar to see such a patient with acute blood loss shortly thereafter become jaundiced and develop ascites. However, in this patient the stools were guaiac negative, the ascitic fluid was not bloody, and the hemoglobin was 11 gm per 100 cc. Hence I will dismiss this possibility.

A final consideration, and the one that I think is most likely, is thrombosis of the portal or hepatic veins or possibly of the vena cava. This could account for the sudden development of ascites and jaundice and for the high white-cell count and likewise for the rapid death. Such a thrombosis is sometimes caused by a hepatoma encroaching on the lumen of the vessels. There is little on which to base such a supposition in this case.

I will conclude that the patient had portal cirrhosis. I do not believe the episode leading to her death in hepatic failure was an acute yellow atrophy. The precipitating incident may have been thrombosis of the hepatic portal vein.

DR DONALD S. KING: I saw this patient in the wards for several days before she died. My opinion was that autopsy would show some areas of acute necrosis in the liver in spite of the fact that it was enlarged and apparently hard. I notice that the house officer also suggested that thrombosis would be found at autopsy. We had not thought much about that on the ward. We tried to explain the fever and high white-cell count and diarrhea. We were surprised at the gross autopsy findings, although I do not know what the microscopical findings were.

DR JOHN HOGAN: Have you seen this electrolyte disturbance in cases of liver disease frequently? The patient was not on salt restriction.

DR FAIRLIE: The numerous cases that came to mind have been the result of therapy, but in a patient with an inadequate diet I believe it could occur even without strict limitation of sodium intake.

CLINICAL DIAGNOSES

Laennec's cirrhosis, ? hepatoma of liver
Cholemia

Thrombosis of portal or hepatic vein?

DR FAIRLIE'S DIAGNOSES

Portal cirrhosis

Thrombosis of portal or hepatic vein

ANATOMICAL DIAGNOSES

Cirrhosis of liver, alcoholic type, acutely progressive

Hyperplasia of bone marrow, marked

Extramedullary hematopoiesis, spleen

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: Autopsy showed a large, firm, pale and fatty liver, which at first glance seemed smooth but which, when viewed with oblique lighting, could be seen to be finely granular. It cut with resistance, however, and was obviously much tougher than normal. The spleen was only slightly enlarged, weighing 200 gm., and esophageal varices were questionable in our opinion, although I think the x-ray verdict is probably more accurate than ours, since we only see the specimens in the collapsed state. There was nothing else in the gross examination that was particularly remarkable, except the adrenal glands, which were quite swollen, and the bronchi, which contained some purulent exudate.

Microscopical examination of the liver showed a very acutely progressive cirrhosis of the type that we commonly see in alcoholic patients, with moderate amounts of fat and slight diffuse fibrosis, but with a great many cells showing hyaline degeneration and a very unusual degree of infiltration of the liver with polymorphonuclear leukocytes, particularly in the portal areas and about the degenerating liver cells. I would describe it as an alcoholic cirrhosis progressing almost at a fulminating rate—as marked as I have ever seen.

One other surprise was provided by microscopical examination of the bone marrow and spleen. The bone marrow was intensely hyperplastic, with hyperplasia of the red-cell series and quite a considerable proportion of rather primitive cells. It was slightly suggestive of what one sees in pernicious anemia. The spleen also was full of foci of hematopoiesis. I do not know of any certain way of connecting the liver disease and the bone-marrow findings and am inclined to think that the bone marrow was another evidence of dietary deficiency in this patient, rather than being due to the liver condition.

DR BENJAMIN CASTLEMAN We have had several patients with so-called acute alcoholic cirrhosis with white-cell counts of 40,000

DR MALLORY Yes, the count can run very high I do not think we have seen a bone marrow as active as this, and never extramedullary hematopoiesis

DR MADELAINE BROWN I do not suppose you removed a peripheral nerve, did you?

DR MALLORY Yes, we did, but the neuropathologist has not yet reported upon it

DR HOGAN The adrenal glands were normal microscopically?

DR MALLORY There was lipoid depletion and swelling of the pseudotubular type It is a non-specific type of response that one sees in most infectious diseases, as well as in a great variety of noninfective diseases

CASE 35282

PRESENTATION OF CASE

A forty-eight-year-old man entered the hospital complaining of headache and intermittent vomiting for two weeks (The history was obtained from the patient's wife because he was drowsy)

Three and a half weeks before admission he sprayed his apple orchard with a mixture of lead arsenate and DDT, about 35 gallons were used Three weeks before admission he had an occipital headache, which lasted two days and was relieved by aspirin A few days later he again sprayed the trees with the same mixture The spray nozzle broke, and the patient was drenched with the solution He changed his clothes and finished his work Two weeks before admission the occipital headache recurred and was more severe On the following day he started vomiting in a projectile fashion His doctor found him afebrile, with a strong, slow pulse Urinalysis showed a few red blood cells The occipital headache continued, and the patient became lethargic, sleeping most of the time Ten days before admission he complained of dizziness and weakness on trying to get out of bed and inability to see well without his glasses Three days later he was admitted to another hospital, where the general physical examination demonstrated no abnormalities Positive neurologic findings included moderate weakness in the grip of the right hand and weakness of the right leg, but there was no wrist or foot drop The right knee jerk was greater than the left The blood pressure was 128 systolic, 80 diastolic, and the pulse 68 The red-cell count was 5,000,000 on two examinations Two of three blood smears examined reported stippling in 1-400 and 1-500 cells Five days before admission he seemed irrational and could not answer questions or carry on conversation On the third and second days be-

fore admission he received BAL, and his symptoms cleared up slightly He was transferred to the Massachusetts General Hospital for further study

The patient had always been in excellent health until the onset of the present illness except for moderate deafness, present from the age of nineteen This had been treated recently with pyribenzamine, with some symptomatic relief

On admission the patient was drowsy and apathetic The general physical examination was negative except for a pilonidal sinus The initial neurologic examination demonstrated extreme nuchal rigidity, a negative Kernig sign, bilateral papilledema of two diopters and flaccid paralysis of the right arm and leg, with hypoactive right deep tendon reflexes and normal sensation

The temperature was 99°F, the pulse 90, and the respirations 18 The blood pressure was 122 systolic, 82 diastolic

Examination of the urine was negative, a test for arsenic was also negative Examination of the blood showed a white-cell count of 17,000, with 90 per cent neutrophils, 3 per cent lymphocytes, 6 per cent monocytes, and 1 per cent eosinophils Occasional stippling of the red cells was noted The hemoglobin was 14.5 gm Chemical examination of the blood demonstrated a non-protein nitrogen of 37 mg, a total protein of 6.6 gm, a calcium of 10.6 mg, a phosphorus of 4.5 mg and an alkaline phosphatase of 5 mg per 100 cc The chloride was 100 milliequiv per liter On lumbar puncture the initial spinal-fluid pressure was equivalent to 285 mm of water, and after 10 cc of clear, colorless fluid was removed it was equivalent to 95 mm of water The total white-cell count was 21 per cubic millimeter, with 7 lymphocytes and 14 polymorphonuclear leukocytes Globulin reaction was positive, and the sugar was 110 mg per 100 cc, the chloride 124 milliequiv per liter, and the total protein 84 mg per 100 cc The fluid was sterile

The patient was placed on BAL therapy, 250 mg 6 times a day intramuscularly, a high-calcium diet, calcium levalinate (1 amp intravenously three times a day for two days), syrup of sodium citrate (2 gm orally four times a day) and 1000 cc of 5 per cent dextrose and water For the first three hospital days the patient became more stuporous, drowsy and disoriented The speech became slurred, he responded to commands slowly and often inaccurately On the third day neurologic examination showed severe nuchal rigidity and left external rectus weakness, the left eye remaining almost in midposition when the right eye was markedly abducted The right hemiparesis was severe, involving the proximal as well as the distal muscles, with marked loss of tone and diminished reflexes No definite facial weakness or anesthesia and no gross sensory loss were detected

other respects. That would be unusual for acute yellow atrophy. The liver was large and very firm, which would likewise be unusual. Further support for the presence of long-standing liver disease is found in the fifteen months' history of nonspecific symptoms and the history of poor nutrition, probable alcoholism and probable esophageal varices.

We thus come to the conclusion that she had portal cirrhosis. What, then, caused her sudden decline? One of the common phenomena that cause cirrhotic patients to become decompensated is infection. This can be an infection of any kind. Even a brief episode of gastroenteritis can be responsible. The white-cell count suggests infection in this patient, but there were no localizing signs. I suppose it could have been a hidden infection, such as mediastinitis, or a deep phlebitis. But there is no reason to think of such entities except that we are searching for infection. Under the heading of infection should be mentioned viral hepatitis. It is uncertain how large a part viral infection of the liver plays in the course of chronic liver disease due to other conditions.

Another common incident precipitating hepatic failure in cirrhotic patients is hemorrhage. It is familiar to see such a patient with acute blood loss shortly thereafter become jaundiced and develop ascites. However, in this patient the stools were guaiac negative, the ascitic fluid was not bloody, and the hemoglobin was 11 gm per 100 cc. Hence I will dismiss this possibility.

A final consideration, and the one that I think is most likely, is thrombosis of the portal or hepatic veins or possibly of the vena cava. This could account for the sudden development of ascites and jaundice and for the high white-cell count and likewise for the rapid death. Such a thrombosis is sometimes caused by a hepatoma encroaching on the lumen of the vessels. There is little on which to base such a supposition in this case.

I will conclude that the patient had portal cirrhosis. I do not believe the episode leading to her death in hepatic failure was an acute yellow atrophy. The precipitating incident may have been thrombosis of the hepatic portal vein.

DR DONALD S. KING: I saw this patient in the wards for several days before she died. My opinion was that autopsy would show some areas of acute necrosis in the liver in spite of the fact that it was enlarged and apparently hard. I notice that the house officer also suggested that thrombosis would be found at autopsy. We had not thought much about that on the ward. We tried to explain the fever and high white-cell count and diarrhea. We were surprised at the gross autopsy findings, although I do not know what the microscopical findings were.

DR JOHN HOGAN: Have you seen this electrolyte disturbance in cases of liver disease frequently? The patient was not on salt restriction.

DR FAIRLIE: The numerous cases that came to mind have been the result of therapy, but in a patient with an inadequate diet I believe it could occur even without strict limitation of sodium intake.

CLINICAL DIAGNOSES

Laennec's cirrhosis, ? hepatoma of liver
Cholemia
Thrombosis of portal or hepatic vein?

DR FAIRLIE'S DIAGNOSES

Portal cirrhosis
Thrombosis of portal or hepatic vein

ANATOMICAL DIAGNOSES

Cirrhosis of liver, alcoholic type, acutely progressive
Hyperplasia of bone marrow, marked
Extramedullary hematopoiesis, spleen

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: Autopsy showed a large, firm, pale and fatty liver, which at first glance seemed smooth but which, when viewed with oblique lighting, could be seen to be finely granular. It cut with resistance, however, and was obviously much tougher than normal. The spleen was only slightly enlarged, weighing 200 gm., and esophageal varices were questionable in our opinion, although I think the x-ray verdict is probably more accurate than ours, since we only see the specimens in the collapsed state. There was nothing else in the gross examination that was particularly remarkable, except the adrenal glands, which were quite swollen, and the bronchi, which contained some purulent exudate.

Microscopical examination of the liver showed a very acutely progressive cirrhosis of the type that we commonly see in alcoholic patients, with moderate amounts of fat and slight diffuse fibrosis, but with a great many cells showing hyaline degeneration and a very unusual degree of infiltration of the liver with polymorphonuclear leukocytes, particularly in the portal areas and about the degenerating liver cells. I would describe it as an alcoholic cirrhosis progressing almost at a fulminating rate—as marked as I have ever seen.

One other surprise was provided by microscopical examination of the bone marrow and spleen. The bone marrow was intensely hyperplastic, with hyperplasia of the red-cell series and quite a considerable proportion of rather primitive cells. It was slightly suggestive of what one sees in pernicious anemia. The spleen also was full of foci of hematopoiesis. I do not know of any certain way of connecting the liver disease and the bone-marrow findings and am inclined to think that the bone marrow was another evidence of dietary deficiency in this patient, rather than being due to the liver condition.

In favor of a tumor of the brain he had had a repeated history of several weeks of progressive drowsiness, headache, choked disks and signs of increased intracranial pressure. There is one point about dealing with the spinal-fluid pressures, the Ayala index—I do not use this index very often, but it may help here. The quantity of fluid removed is multiplied by the final pressure, and the product is divided by the initial pressure. If the ratio is over 5, it is supposed to indicate a diffuse cerebral lesion, with increased spinal-fluid volume. When it is under 5 it is supposed to indicate a space-occupying lesion. With these spinal fluid findings— $\frac{10 \times 95}{285}$ —we have a low index, 3.3,

which goes with tumor, probably in the posterior fossa. The spinal-fluid protein of 84 gm per 100 cc and the positive globulin are consistent with tumor. The neurologic signs are interesting in that on the third day there was weakness of the left external rectus muscle and right hemiparesis, which suggest that the lesion was near the midbrain but outside it. The air studies suggest something displacing the aqueduct to the left and forward. I think that would be unusual in any poisoning. It suggests tumor in the posterior fossa with pressure in that region. The stiffness of the neck is also consistent with posterior-fossa tumor. Just before death the reduction in reflexes and the hyperthermia would also be associated with a posterior-fossa lesion. A tumor or an aneurysmal sac would be the two things that one would think of. It seems to me, therefore, that the weight of evidence is against poisoning, although I cannot explain the stippling. I should say that he had a lesion of the left posterior fossa near the midline. The x-ray evidence puts it on the other side, which would involve the pyramidal tract from the right hemisphere. Another point worth mentioning is that the seventh-nerve pyramidal fibers cross at the level of the third-nerve nucleus, which would be above the area involved by this lesion. Hemiplegia involving the arm and leg without involving the face is consistent with a posterior-fossa lesion of the left side.

A PHYSICIAN: Would you consider a secondary metastasis to the brain?

DR SCHWAB: Yes. The data indicated no primary source for the tumor, and the lungs were normal. When I said "tumor" I did not say what kind. It may have been a metastatic tumor. This was a fairly rapidly growing one, it could have been either.

DR WILLIAM H SWEET: On the ward a nice and lively discussion ensued in this case. From the ventriculograms I said that there was evidence of a space-taking lesion, on the right side of the

posterior fossa. Our neurologic colleagues thought that the clinical picture was not sufficiently suggestive of that and took the patient back on their service. I think this case is important to point out again that if one does a ventriculogram, and demonstrates by that procedure a probable neoplasm, there is often very little time remaining for a discussion. The patient must be taken promptly to the operating room, and the neoplasm, if present, treated immediately. In this case we consider that even if there had been a lead encephalopathy, proper treatment was a suboccipital craniectomy for decompression. In the lone case in my personal experience in which lead encephalopathy was so handled the outcome was satisfactory.

CLINICAL DIAGNOSIS

Tumor or abscess of brain

DR SCHWAB'S DIAGNOSIS

Tumor, left posterior fossa

ANATOMICAL DIAGNOSES

Carcinoma of ascending colon, with metastases to brain, liver, lung and lymph nodes

Arteriosclerosis, generalized, slight

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY: Autopsy in this case showed something that would not be remotely suggested by the record. The patient had a primary cancer of the ascending colon, with widespread metastases throughout the body.

DR SCHWAB: Was there nothing in the lungs?

DR MALLORY: Multiple metastases were present in the lungs, which I think should have been demonstrated by x-ray examination. The liver was full of them. As far as the central nervous system is concerned, we found two tumors in the cerebellum—one in the right and one in the left hemisphere. There were two other intracerebral tumors, one in the left parietal and one in the right temporal lobe.

DR SCHWAB: The right temporal and left parietal metastases were apparently silent. Can you see anything in the chest, Dr Wyman?

DR WYMAN: I do not see any pulmonary metastases. It is interesting to point out that it is not uncommon to have extensive lesions that cannot be demonstrated on the films. Tuberculosis is certainly a common offender. Could the tumors have caused displacement of the lateral ventricles toward the right in the anteroposterior films?

DR MALLORY: I think they could have.

DR SCHWAB: Was that a large lesion in the parietal lobe?

DR MALLORY: No—slightly under 1 cm in diameter.

X-ray films of the skull, right hand and arm and a posteroanterior film of the chest were normal. An electroencephalogram showed a diffusely abnormal record, with moderately slow activity, a little more marked on the left than on the right side of the head, especially in the central and, to some extent, the parietal region. The temperature, pulse and respirations went up to 102°F, 130 and 28, respectively. A lumbar puncture on the same day showed an initial spinal-fluid pressure equivalent to 340 mm of water, with 12 polymorphonuclear leukocytes and 3 lymphocytes per cubic millimeter. The patient was started on penicillin, 100,000 units every three hours intramuscularly, and given 10,000 units of penicillin intrathecally at the time of the lumbar puncture. A ventriculogram on the fourth day showed slightly dilated lateral ventricles, a little more marked on the right. The third ventricle was slightly dilated. The aqueduct and fourth ventricle showed a slight shift to the left, and the aqueduct was also displaced slightly forward. During the day his condition became worse, with a return of rapid pulse to 140, a gradual rise in temperature to 103.6°F and a continued comatose condition.

At 5:30 p.m. that day he suddenly became cyanotic, with shallow breathing. Oxygen and artificial respiration were started. A ventricular tap showed clear spinal fluid under increased pressure. He died at 5:40 p.m.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT S. SCHWAB: Did this man develop the occipital headache before or after the spraying episode, when the nozzle of the hose broke? I think that is an important question.

DR. WILLIAM H. SWEET: It occurred after the nozzle broke.

DR. SCHWAB: I should like to look at the x-ray films. Where is the pineal body?

DR. STANLEY M. WYMAN: I cannot demonstrate it on the anteroposterior or posteroanterior films. In the lateral film it appears to be approximately in the normal position.

DR. SCHWAB: I am interested in the statement that the aqueduct was displaced forward and to the left.

DR. WYMAN: The displacement of the aqueduct is best seen in this posteroanterior view. The third ventricle is dilated, lying close to the midline, the aqueduct extending a little toward the left. We filled part of the left ventricle, the right does not seem to fill. The displacement anteriorly is best seen in the occipital position, and the aqueduct can be seen starting horizontally and taking a sharp bend caudally, with a 90° angle at this point. The fourth ventricle is definitely filled. The distal portion of the aqueduct is displaced anteriorly and to the left.

DR. SCHWAB: Is the pineal body in normal position in spite of the displacement of the aqueduct?

DR. WYMAN: I cannot see any shift of the pineal body in the anteroposterior view.

DR. SCHWAB: The essential clinical findings in a man forty-eight years old with headache, projectile vomiting, stupor and hemiparesis at once suggest intracranial tumor. On the other hand the history given by his wife makes me think of poisoning from heavy metals or DDT. The differential diagnosis is therefore between poisoning from lead, arsenic or DDT, so-called toxic encephalopathy and tumor. In favor of the diagnosis of poisoning is the temporal relation of this unusual simultaneous exposure to arsenic, lead and DDT (in a 35-gallon amount) some three weeks before admission to the hospital. On the other hand, there is a clue in the statement that the headache in the occipital region came on before he was covered with liquid when the spray nozzle broke. It may be a false clue however. There are several points against poisoning. He was covered with liquid, but he took off his clothes and presumably washed himself so that there was no chronic exposure. He might not have swallowed any of the mixture. For the diagnosis is the report of a small amount of stippling, 1-500 only, on two smears. Outside these two items the picture is not characteristic of heavy metal poisoning. Against poisoning with metals is the fact that there were no urinary symptoms such as hematuria or albuminuria, which almost always occur in heavy-metal poisoning of the acute type. Also, there was no anemia and no gastrointestinal symptoms such as diarrhea, cramps, colic, nausea and anorexia. There were no skin findings and no lead line on the gums. Patients with arsenical poisoning have dark skin on the hands but no peripheral signs such as sensory loss and wrist drop, which are found with DDT poisoning. However, I have never seen such a case. The administration of BAL evidently failed to do anything because this man continued downhill rapidly and died in spite of medication for heavy-metal poisoning, which he got in large amounts, and in spite of alkalis in tremendous doses. The spinal fluid does not show evidence of meningitis, such as is associated with arsenical poisoning, in which the cells are usually over 100 per cubic millimeter. The stiff neck and the definite rigidity without a Kernig sign or cells in the spinal fluid make me think of a posterior-fossa lesion rather than a meningitis. Another important finding is that this patient was progressively drowsy with aphasia in the end from pressure but was not delirious and did not have convulsions, which are almost always seen in fatal cases of lead encephalopathy before the terminal stage is reached. We have a whole group of points against the diagnosis of heavy-metal or DDT poisoning.

But the main value of this study is its implication that the descent of the doctor to the level of the gangster can happen in any country. The embracement of the utilitarian philosophy of Hegel, with its corollary of euthanasia, has its counterpart in American society — Dr Alexander cites chapter and verse in the form of the attitude of a physician and a hospital toward patients with chronic degenerative disease, he emphasizes the discussion of sterility and euthanasia at a meeting

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THE PROTECTION OF PERSONNEL ENGAGED IN ROENTGENOLOGY AND RADIOLOGY*

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BOSTON AND CAMBRIDGE, MASSACHUSETTS

WITH recent evidence suggesting that radiologists have a higher death rate from leukemia than their colleagues,^{1,2} protection from the dangerous effects of radiation in the fields of diagnosis, therapy and research becomes a subject of increased importance. Currently, a total exposure dose of 0.3 r per week is the accepted limit of safety.³ But whether this limit is really safe,⁴ or, indeed, whether it has much meaning at all is open to challenge.

It should be apparent that ionizing radiant energy, capable of penetrating to the blood-forming organs, produces quite a different effect upon the body as a whole than radiation that is absorbed for the most part by the skin. This fundamental principle was correctly understood by Mutscheller,⁵ who realized that a long wave-length tolerance dosage did not apply in the shorter wave-length ranges, and called attention to the great length of time required for the accumulation of an injurious dosage of "hard" radiation, and to the long latent period before resulting changes are positively recognized.

In the field of medical radiology, knowledge of radiation hazards has remained particularly unsatisfactory because of the difficulty in making precise determinations of exposure sustained in various diagnostic technics, and because relatively little effort has thus far been made to correlate such continuously repeated exposures with the ultimate biologic response. For these reasons, a program has been undertaken at the Massachusetts General Hospital with the object of establishing a more quantitative basis for relating radiation exposure to morphologic changes in the peripheral blood, and of determining the value, if any, of the peripheral blood picture as an early index of bone-marrow injury.

It was recognized from the start that this study should correlate adequate recorded information on the quantity and quality of radiation received by personnel during routine procedures with progressive blood changes over long intervals. The present communication is therefore a preliminary one. It describes a film badge developed during the course of the investigation that gives quantitative information on both the exposure dose and its quality, presents the results of physical studies made on the direct and scattered radiation to which personnel may be exposed, discusses the significance of these data and comments briefly on some early results of monitoring.

Measurements have been made of the intensity and quality of direct-beam radiation, and of scattered radiation from a phantom irradiated under conditions similar to those present during fluoroscopy. Braestrup,⁷ it is true, has pointed out that "Masonite pressdwood" phantoms are rather inaccurate for measurements of radiation below 200 kvp, but inasmuch as it was considered unwise to expose a particular patient long enough for certain determinations to be made, it seemed advisable to use this convenient material.

The present study has shown that, contrary to generally recorded opinion,⁸ the 90° scattered radiation from a phantom subjected to fluoroscopic radiation is actually more penetrating than the direct beam that produces it. This important but hitherto unappreciated fact has the following physical explanation. The phantom subjected to radiation produced at 50 to 140 kvp behaves as a filter and absorbs most of the "softer" components of the heterogeneous beams. Those scattered x-rays capable of emerging from the depth of such a phantom would be produced chiefly by the Compton-scattering process. Compton-scattered photons, however, are increased in wave length by only 0.024 Ångstrom unit for 90° scattering. This relatively small increase in wave length has little effect on the quality of the more penetrating components of the original beam, the softer components of which have been largely eliminated by absorption. As a result, the total scattered radiation,

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Department of Labor — a mere handful Veterans constitute 47 per cent of all federal employees

There is a certain fascination in the spectacle of a nation strangling itself by paternalism The process can be stopped only by a mass reaction, and yet if it continues the outcome is inevitable

Smallpox is again showing itself in different sections of Maine More persons die of this disease, who are natives of that State, it is asserted, than in all the rest of New England So much for neglecting vaccination

Boston M & S J, July 11, 1849

NOTES FROM THE MEDICAL EXAMINER IDENTIFICATION OF BLOODSTAINS—I

There are few types of evidence that occur with greater regularity at the scenes of crimes of violence and bear implications of greater evidential importance than bloodstains Their recognition and characterization serve to localize the scene of the crime, aid in determining the manner in which it was committed and, if circumstances are favorable, help to identify the perpetrator It is therefore valuable to review current methods of blood identification and their application to legal medicine

The most sensitive tests for blood are those which make use of its catalytic activity in enhancing the oxidation of certain phenols and amines by hydrogen peroxide These reactions, which the benzidine, guaiac and phenolphthalein tests¹⁻³ exemplify, depend upon the blood peroxidase activity, an enzymatic function of the heme portion of the hemoglobin molecule The reactions are extremely sensitive Thin, invisible dried smears, caused by as little as 1 part of blood in 10,000 parts of water, may be detected by the benzidine test,* for example Even garments that have been laundered several times may yield evidence of previous bloodstains

Unfortunately, no one of these tests is by itself specific for blood Vegetable peroxidases, such as those present in horseradish, potato and turnip, cause similar reactions and may be destroyed by boiling, whereas the peroxidase activity of blood is relatively stable But the virtue of the catalytic blood tests, of which the benzidine test is the most generally practical for medicolegal purposes, rests in their high sensitivity and simplicity They are best used for screening purposes, not for proof If the test is negative, blood is absent, if it is positive, blood is suspected The following case provides an example to illustrate the point

A 64-year-old retired businessman, his wife and her elderly sister, who lived in a single house in a residential suburb,

*The benzidine reagent consists of 0.1 gm of benzidine and 0.2 gm of sodium perborate dissolved in 10 cc of 50 per cent acetic acid. It should be prepared immediately before use. An instantaneous blue color indicates blood

had not been seen for several days The apprehension of neighbors having been aroused, the house was entered through a window The 2 women were found in bed beaten to death, and the man hanging by a rope around the neck in the cellar The extent of blood splashes at the scene of the death of the women indicated that their assailant had been blood splattered The man was clean and dressed in a lounging robe and fresh pajamas Benzidine tests of the hands and body of the man revealed abundant evidence of washed blood The wash basin in the bathroom also revealed invisible blood stains The evidence substantiated the fact that the man had committed suicide by hanging after murdering the women

Bloodstains remain detectable on the hands, arms and body of a living person for several days, in spite of ordinary careful washing This fact is of considerable importance in the examination of suspects in murder cases, sex offenses and other bloody crimes of violence The reagent may be applied directly to the skin, or the skin may be swabbed by moistened filter paper, to which the reagent is then applied In examination of a person for bloodstains, it is important to keep in mind the possibility of local stains (without criminal implication) arising from chapped hands or lips, pimples, minor cuts and abrasions

For medicolegal purposes it is desirable to establish the presence of blood with greater certainty than can be done by the catalytic tests Spectroscopic examination and microcrystal tests add confirmatory, and frequently conclusive, evidence Because the spectroscopic examination requires relatively large amounts of blood, it is not applied so frequently as the microcrystal tests The Bertrand⁴ modification of the hemin crystal test[†] and the hemochromogen crystal test[‡] are applicable to any blood particle or stain that can be seen by the naked eye Each test may be carried out on a microscope slide, the resulting crystals being examined under the microscope In favorable cases the characteristic spectral absorption of the hemochromogen crystals may be confirmed by the use of a microspectroscope

†Reagent 1 gm of magnesium chloride 1 cc. of water, 5 cc. of glycine and 20 cc of glacial acetic acid A drop of reagent is added to the blood particle on a microscope slide and covered with cover slip and heated gently, nearly to boiling It is cooled reheated and then cooled and examined under low power Brown rhombic plates of hemin are observed.

‡Reagent 6 cc 10 per cent sodium hydroxide 6 cc. of pyridine 6 cc of saturated solution glucose and 14 cc of water The reagent improves with age and then deteriorates One drop is added to the blood particle on a microscope slide and a cover slip is applied The slide may be warmed very gently to induce crystal formation Characteristic, salmon pink, nearly rhombic plates occur

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(Notices on page xi)

Over an exposure range between 0.005 and 0.14 r for a given radiation quality the net film density, D , beneath any one of the four "windows" was found to be a linear function of the exposure r , as measured in roentgens by an ionization chamber. Thus

$$rk = D \quad (1)$$

where k is a constant determined by both the filter and the film emulsion employed.

Moreover, each filter transmits monochromatic radiation in accordance with the equation

$$r/r_0 = e^{-\mu x} \quad (2)$$

where r_0 and r are the initial and final values, x is the thickness of the filter in cm, μ is the absorption coefficient of the particular material and e is the base of natural logarithms. And since an equation of similar form describes the absorption of a heterogeneous beam of radiation, such a beam of rays may be represented by a single "effective" wave length on which the filter produces equivalent attenuation.

The relations in equations (1) and (2) may therefore be applied to the film densities produced under the aluminum and steel filters. Since the incident radiation r_0 is the same for both filters we find that

$$\log D_a/D_s = \mu_s x_s - \mu_a x_a \quad (3)$$

where the subscripts denote aluminum or steel.

For filters of fixed thickness the difference between the two terms on the right-hand side of equation (3) in spectral regions with no absorption discontinuity is determined by the wave length in the case of monochromatic radiation, or by the "effective" wave length in the case of a heterogeneous beam. Hence the log ratio of the film density beneath any pair of "windows" — for example, aluminum and steel — is a measure of the quality of radiation and is independent of the quantity. The quality of the radiation used in this study has been specified both in terms of the log of the film-density ratio under the aluminum and steel windows ($\log D_a/D_s$) and in the conventional form of half-value layer (hvl) of aluminum.

Advantages of film badges. Study was made of the comparative value of pocket ionization chambers and filtered film badges for measuring the radiation received by personnel over a period of two weeks. This led to the selection of film badges for the following reasons:

The use of an open "window" and three metal filters permits an adequate determination of radiation exposure and quality on a single film.

With a photoelectric spectrophotometer capable of isolating a narrow wave-band width (140 Å at 5600 Å), reproducibility of film-density readings was found to be 2 per cent or better.

Stock dental films (Du Pont No. 550) thus exposed to diagnostic x-rays are capable of giving a measurable indication of heavy radiation exposure and, in the exposure-range of greatest interest (0.01 r to 0.14 r), show a linear relation between film density and total roentgens received.

By means of special sensitive films (Du Pont No. 552) exposure to kilovoltages above 200 and to gamma radiation can be similarly quantitated.

Unlike ionization-chamber electrometers, dental films are less subject to individual variations in sensitivity and do not give rise to errors from electrical leakage.

The film badge is more conveniently worn, and the developed film furnishes a permanent record.

Disadvantages of film badges. Film badges are inconvenient in two respects: fresh standards must be made whenever a new film emulsion is used, and

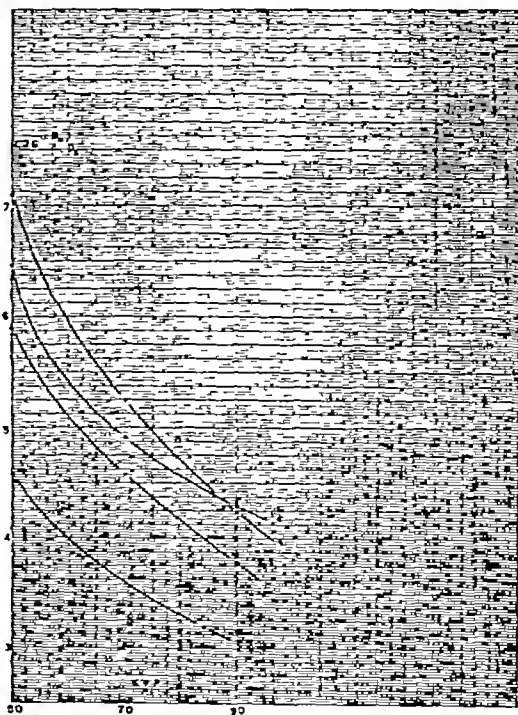


FIGURE 2 Quality Measured by Film Badges ($\log D_a/D_s$) 1-mm Aluminum Filtration

a, b, c = direct beam with different film emulsions, c' = side scatter with film emulsion the same as c

they must be prepared by exposure to the particular type of radiation to be measured. Figure 2 shows $\log D_a/D_s$ values for three different film emulsions obtained in the direct beam 8 feet from the target at kilovoltages of 50, 70 and 90, and with a filtration of 1.0 mm of aluminum. As these curves show neither parallelism nor consistent differences, it

though greatly reduced in intensity, has its average wave length shifted closer to the minimum wave length of the direct beam. Such scattered radiation must therefore be regarded as capable of reaching the blood-forming organs of the examiner in significant amounts.

Figure 1 (calculated from Ulrey⁹) shows the attenuation of intensity and the displacement of the average wave length of the 50 kvp tungsten spectrum toward the shorter wave-length region

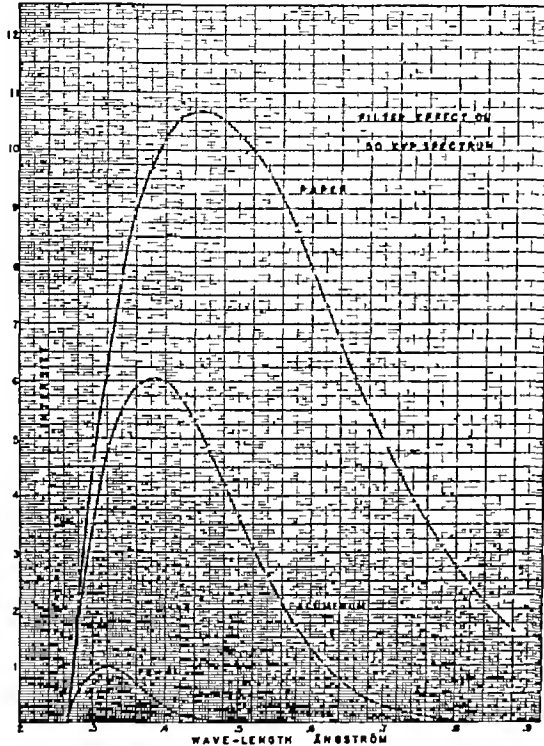


FIGURE 1 The 50 Kvp Tungsten Spectrum

Attenuation of intensity and displacement of the average wave length toward the shorter wave-length region by filtration (modified from Ulrey⁹)

by filters of 10 mm of paper (carbon), 10 mm of aluminum, and by the steel-aluminum "window" of the film badge described below. These curves clearly illustrate how selective absorption of the "softer" components results in radiation with a "harder" average quality than that of the original heterogeneous beam.

MEASUREMENT BY IONIZATION CHAMBERS AND FILM BADGES

Ionization Chambers

Comparative studies were made of the suitability of several types of ionization chambers for intensity measurements in the kilovoltage range from 50 to 140. It was recognized that for the lower

voltages care must be taken to avoid excessive wall thickness, not only because of the softness of the radiation but also since the reading would be relatively more dependent on the atomic constituents of the "air-wall" material.

The instruments eventually used were Victoreen chambers of 250r and 0.25r capacity and two 0.2r full-scale pocket electrometers of the minometer type. Because eight minometers in test exposures showed rather large variations in individual sensitivity, two that gave the most consistent readings were employed in all the experiments. It was found that the 0.25r Victoreen chamber and this pair of minometers gave equivalent readings for 70 kvp and above. But in the region below 70 kvp, the minometer chambers showed advantages, presumably because of the thinner wall of the thimble. Finally, to reduce measurement errors to a minimum, in most of the experiments film badges and one or both types of ionization chambers were exposed simultaneously to the radiation.

Film Badges

Film-badge characteristics. To distinguish between the wide range of wave lengths characteristic of diagnostic roentgenology and therapeutic radiology, a film badge, similar in some respects to the one used by Braestrup,¹⁰ was provided with four filters or "windows." After a number of trials the following filters proved satisfactory: 1.015 mm (0.040") cadmium, 0.254 mm (0.010") tool steel plus 0.762 mm (0.030") aluminum*, 1.015 mm (0.040") aluminum, and an open "window." In order to prevent rusting, the steel filter was "gun-metalled" by treatment with ammonium polysulfide. Small holes drilled through one end of the cadmium filter were spatially arranged to form a code number. Before removal of the film for development, the remainder of the badge could be covered with lead, and the code number recorded for identification purposes on the film beneath the cadmium window with low-voltage x-ray.

In processing films, remarkably consistent results were obtained when the following technique was meticulously carried out. A fresh solution is made each time a series of films with unexposed controls is to be developed. A 1-gallon-size can of Eastman rapid-developing powder is dissolved in 2 gallons of water in a glass jar. When the solution has been stirred well and the temperature adjusted to exactly 68°F, the films are developed for exactly six minutes, being agitated once or twice meanwhile. After being rinsed the films are placed in hypo for ten minutes, and then they are washed for twenty minutes and dried. (After the films had been placed in the hypo, it was found the light should not be turned on until two minutes had elapsed.) Calibration against an r-meter must be made for each film-emulsion lot-number.

*Henceforth this filter is referred to as the steel filter.

QUALITY MEASUREMENTS WITH FILM BADGES OF
SIDE SCATTER BETWEEN 50 AND 90 KVP

Early in the study it became evident that x-ray quality as measured by film badges ($\log D_a/D_s$) was considerably "harder" for 90° scatter from the phantom (point C) than for the direct beam itself. This is illustrated in Figure 2 in which c is a $\log D_a/D_s$ curve for the direct beam at 50, 70 and 90 kvp, and c' is the corresponding one for side scatter at 50 and 84 kvp — both sets of measurements being made with films of the same emulsion number. Under the open "window," on the other hand, the net film density for the same r value at these different voltages was practically unchanged, whereas $\log D_a/D_s$ decreased as the kvp rose. Hence, in monitoring, total r received could be determined from the open "window" density, and the quality from the log ratio of the aluminum and steel densities.

Observations were also made on the quality of scatter at different positions lateral to the phantom, namely, 7.5 and 12.5 cm toward the side of the table, 7.5, 9.0 and 12.5 cm toward the foot of the table, and at the Bucky slot after removal of the phantom. With a 20-by-20-cm field, filtration of 1.67 mm of aluminum, and 84 kvp, quality as determined by $\log D_a/D_s$ values was relatively the same for all points enumerated.

EFFECT OF FIELD SIZE ON INTENSITY AND QUALITY
OF SIDE SCATTER

The factors used in making the following measurements were 85 kvp, 4 ma and 1.67 mm of aluminum filtration. Figure 4 shows the results of varying the field size. When the center of a square field coincides with the center of the phantom (C'), side-scatter intensity increases with the area of the field (the square of the field dimension). However, when the margin of a square field is kept at a fixed distance within and close to (2.5 cm) the phantom edge (C), intensity, while initially much greater, increases somewhat less than linearly with the field dimension. These findings are in accord with measurements made by Cilley, Leddy and Kirklin,¹² who have emphasized the protective value of maintaining at all times a minimal field size.

In contrast to these intensity variations, there is no change in side-scatter quality, as measured by film badges, when the centered field (C') is increased from 10 by 10 to 20 by 20 cm. Moreover, the quality of scatter from the 15-by-15-cm field is the same either centered (C') or near the phantom edge (C). As pointed out below, this side scatter is quite "hard," and has a half-value layer of 5.9 mm of aluminum. It is therefore more important than ever to keep the field size as small as possible when a patient is being fluoroscoped.

COMPARATIVE STUDIES OF DIRECT BEAM AND 90°
SIDE SCATTER*

Effect of Filtration on Intensity and Quality at 85 Kvp

Figure 5 shows the effects of filtration on intensity at the points denoted as A, B and C, in Figure 3. In addition, curve A' gives intensity values on the table top when the phantom resting on the instruments produces back scatter. It will be noted that after the addition of 3 mm of aluminum, intensities at A and A' decrease more and more slowly, but that intensities at B and C' continue to fall.

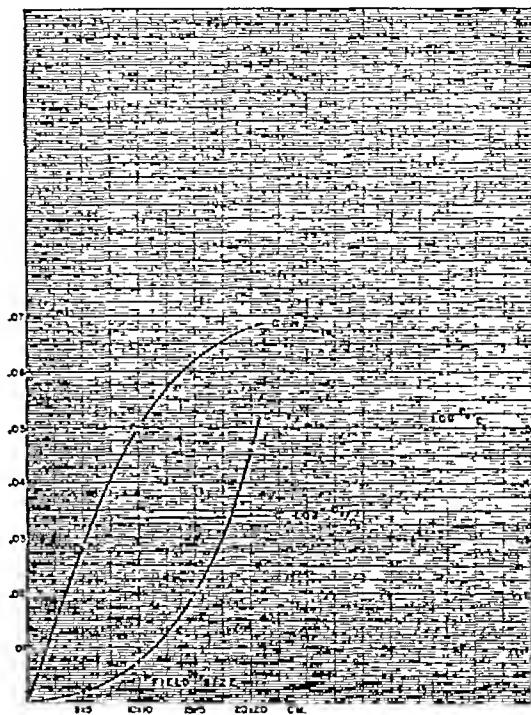


FIGURE 4 Effect of Field Size on Intensity (r per Minute) and on Quality ($\log D_a/D_s$) of Side Scatter 85-kvp, 4-ma, 1.67-mm Aluminum Filtration
 C = field margin 2.5 cm inside phantom edge
 C' = field margin 7.5 cm inside phantom edge (field and phantom centers coincide)

at a relatively constant rate. From this it seems that 3 mm of aluminum is about the optimal filtration in respect to intensity for fluoroscopic purposes.

Although these findings are somewhat at variance with those of Morgan,¹² they correspond closely enough to have significance. A filtration of 3 mm instead of 1.5 mm of aluminum does not noticeably diminish the luminescence of the fluoroscopic screen, yet it does decrease the exposure of the patient (35 per cent), and reduces to some extent (20 per cent) the intensity of the side scatter received by the examiner.

*The x-ray source was a Picker therapy machine with a 'Thermax tube.

is apparent that measurements made with one film emulsion cannot be referred to standards made with a different one. This drawback, however, can be minimized if one obtains a supply of the same film emulsion sufficient for a period of several weeks.

Because scattered x-radiation has a "harder" quality than the generating direct beam, standards for the measurement of scatter must be obtained by simultaneous exposure of film badges and minometers to an arbitrarily selected source. For moni-

ARRANGEMENT OF INSTRUMENTS

Figure 3 shows diagrammatically the general arrangement of tube, table and phantom, and the position of ionization chambers and badges in the experiments to be described. In all cases the phantom was composed of layers of "Masonite pressed wood," with over-all dimensions of 30 by 30 by 15 cm. Except in field-size studies the x-ray field was 15 by 15 cm, measured on the phantom top. The diagram shows the field centered so that the margin of the field is 2.5 cm inside the phantom edge. This field position was employed in the early studies, and is now the standard arrangement when film badges are calibrated for monitoring purposes. However, in the series of observations on filtration and on kilovoltage effects between 50 and 140 kvp, the field was centered on the center of the phantom.

At the point marked *A*, minometers were placed on the table surface with the phantom resting on top of them, in order to measure the intensity on the patient's skin when subject to direct beam and back scatter. (This is designated on the charts as *A'*). Because the back of the film badge was made of steel, and dental films carry a thin foil backing consisting of lead, antimony and tin, quality measurements at this site (to include back scatter) could not be made by means of films. Quality was determined, however, by both minometers (*h1*) and badges on the table top after removal of the phantom (*A*). Position *B*, directly on top of the phantom, represents the position of the palpating hand of the roentgenologist or the location of the fluoroscopic screen. Measurements were also made at *B'*, 12.5 cm above the phantom, but because these figures merely supplement the data obtained at *B*, they have not been presented. Lastly, both *C* and *C'* represent the position at the side of the table where the roentgenologist's lower torso comes nearest to the table edge, *C* indicates that the field margin is 2.5 cm from the phantom edge, and *C'*, that the field is centered on the phantom's center. Although these sites for the instruments were recognized as being somewhat arbitrary, it was believed that they were critical points where radiation should be measured.

For convenient reference, these arrangements of the instruments and apparatus are listed

- A* = table top without phantom (no back scatter)
- A'* = table top with phantom (back scatter)
- B* = phantom top
- B'* = 12.5 cm above phantom
- C* = side scatter, field 2.5 cm from the phantom edge
- C'* = side scatter, field 7.5 cm from the phantom edge (field and phantom centers coincide)

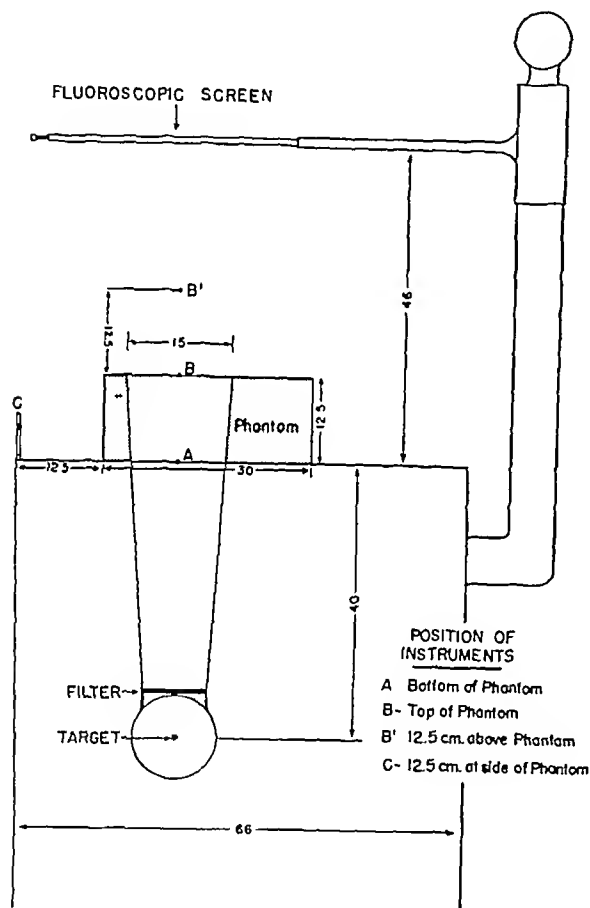


FIGURE 3 Arrangement of Apparatus and Instruments (Viewed from the Foot of the Fluoroscopic Table)

toring purposes, an easily reproducible and convenient source proved to be at a point 90° lateral to and 12.5 cm from a phantom placed on a fluoroscopic table, with the field margin 2.5 cm from the phantom edge, a filtration of 15 mm of aluminum, and a kvp of 85 (Fig 3 *C*). These filtration and kvp factors were chosen because of their general employment in fluoroscopic procedures. This site for the film badge was selected, because it approximates the position of the roentgenologist's lower torso when he is fluoroscoping a patient, and is the point of greatest intensity of scattered radiation.¹⁰

Effect of Voltage on Intensity and Quality with 1.5-mm Aluminum Filtration

Figure 8 shows the intensity at points *A*, *A'*, *B* and *C'*, for kvp values between 50 and 140. At *B* the intensity is about 10 times, and at *A*, it is 150 to 200 times that at *C'*. As presented in the figure, these data merely show that intensity increases with the kilovoltage, but when normalized to give a constant intensity falling on the fluoroscopic screen (Fig 8*A*), other useful information is obtained.

Intensity at *A'* now decreases rapidly and linearly from 50 to 105 kvp, but falls more and more slowly with further increase of kilovoltage. At *C'*, on the other hand, intensity rises slowly and almost linearly up to 105 kvp, and then increases at a continuously accelerated rate. In other words, raising the kilo-

corresponding kvp values are plotted (Fig 9), a linear relation obtains in the 85–140 kvp range, whereas $\log D_s/D_r$ values, similarly plotted, result in a series of hyperbolic curves (Fig 10). Between 50 and 85 kvp radiation quality measured both by hvl determinations and by the film method shows persistent irregularities. Moreover, the quality

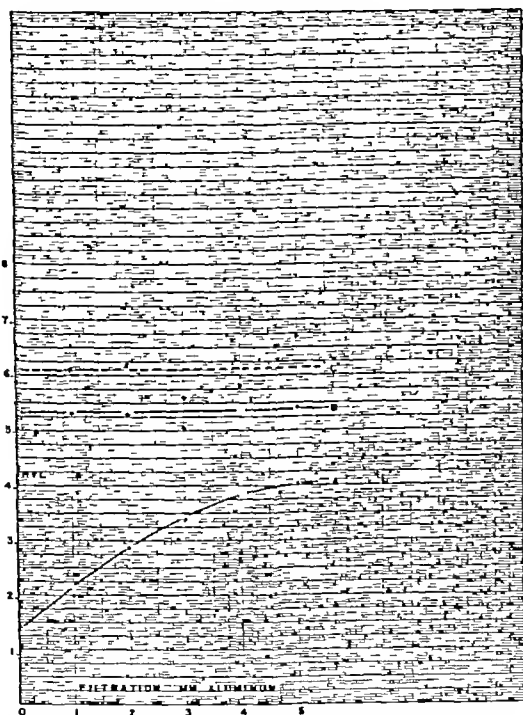


FIGURE 6 Effect of Increasing Filtration with Aluminum on the Half-Value Layer (hvl) 85 kvp, 5 ma

A = table top (without back scatter)
B = phantom top
C' = side scatter (phantom and field centers coincide)

voltage above 105 increases (percentage-wise) the dosage rate of the examiner more than it decreases the dosage rate on the skin of the patient. From this it follows that optimal kilovoltage must lie within the 85–105 kvp range — provided the milliamperage is kept at 5 or below.

The effects of voltage on radiation quality are shown in Figure 9 and 10. When the hvl and the

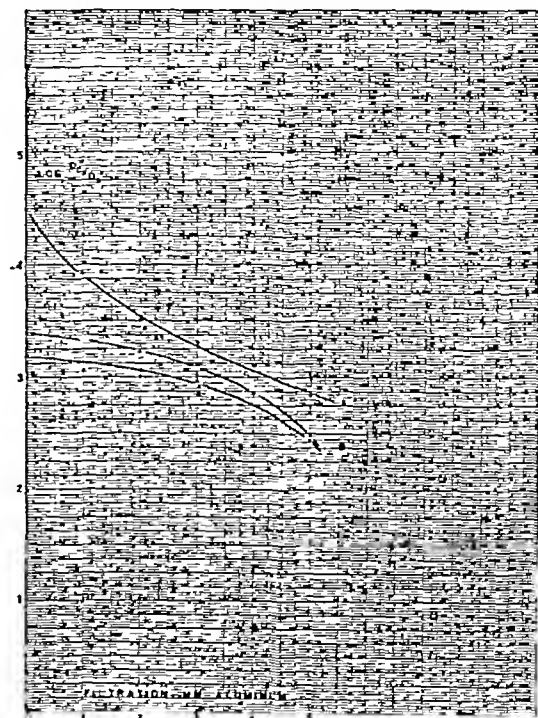


FIGURE 7 Effect of Increasing Filtration with Aluminum on Quality as Measured by Film Badges 85 kvp, 5 ma

A = table top (without back scatter)
B = phantom top
C' = side scatter (phantom and field centers coincide) (Compare with Fig 6)

at 70 kvp in a large number of observations was consistently "harder" than should be expected. As this could not be due to errors of measurement it was presumed to be caused by additional energy of shorter wave lengths emitted at 69 kvp by the tungsten K-series. This phenomenon, however, requires further investigation.

Leddy, Cilley and Kirklin¹³ found that an 85 kvp direct beam, after passing through a 23 cm "Syncrest" wax phantom, had a half-value layer (hvl) of 4.5 mm of aluminum. In spite of differences in primary beam filtration, phantom thickness and phantom material, the half-value layer as measured by these investigators and by ourselves (*B* = 5.25 mm) is of the same order of magnitude.

It should be noted that side scatter at 85 kvp has a half-value layer of 5.9 mm of aluminum, while in the direct beam this value is not reached until

After all, the whole purpose of fluoroscopy is to enable the examiner to visualize contrasting shadows on the screen. Hence, if screen luminescence is satisfactory with 85 kvp, 5 ma and a filtration of 1.5 mm of aluminum, the same screen intensity can be maintained for all thicknesses of filter by varying the milliamperage. The resulting intensity

if hvl values for C' in Figure 6 are compared with corresponding $\log D_s/D_e$ values in Figure 7

From the data presented in these last two figures, increasing the filtration has a relatively slight effect on the *quality* of radiation measured at B and C' , but does have a considerably "hardening" influence on the radiation striking the table top (A). In Figure 6, in particular, hvl values at A obviously approach a maximum above which additional filtration causes practically no further increase. These measurements mean that the phantom so effectively filters out the longer components at B and C' that pre-filtration with extra aluminum does little except to diminish the intensity.

Because nearly maximal "hardness" at A (measured as the hvl) is reached with 3 mm of aluminum, this amount of filtration appears to be

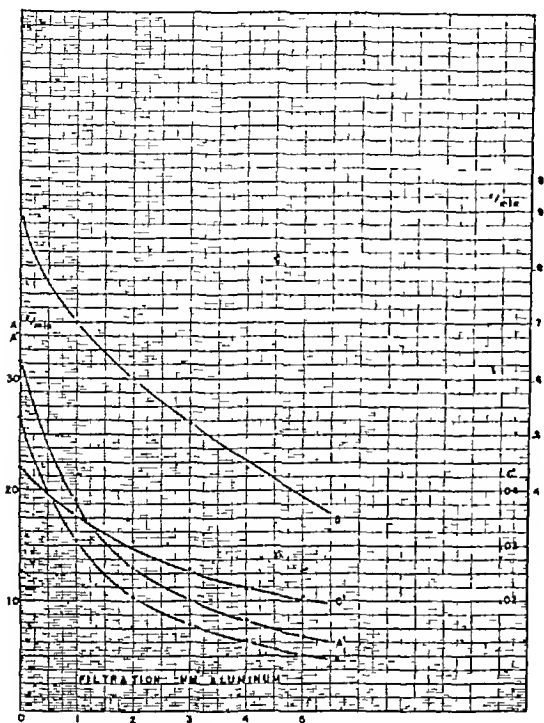


FIGURE 5 Effect of Increasing Filtration with Aluminum on the Dosage Rate (Intensity in r per Minute) 85 kvp, 5 ma, 0 = Intrinsic Tube Filtration

A = table top (without back scatter)
A' = patient's skin-dosage rate (with back scatter)
B = phantom top intensity
C' = side-scatter intensity (phantom and field centers coincide)

values may be obtained by normalizing the data from curves A' and C' (Fig 5) for a constant screen dosage rate (B). These values are shown in Figure 5A. It will be seen that filtration up to 5 mm of aluminum does not affect the dosage rate received by the examiner, but it does attenuate the skin-dosage rate received by the patient—although more than 3 mm of aluminum produces relatively little further attenuation. Therefore this evidence, too, indicates that 3 mm of filtration is about optimal.

The effect of filtration on *quality* was measured both by half-value layer determinations (Fig 6), and by the film-density method, $\log D_s/D_e$ (Fig 7). In practically every instance, quality measurements from films were more consistent and reproducible than corresponding hvl determinations, especially when the intensity was low. This is quite evident

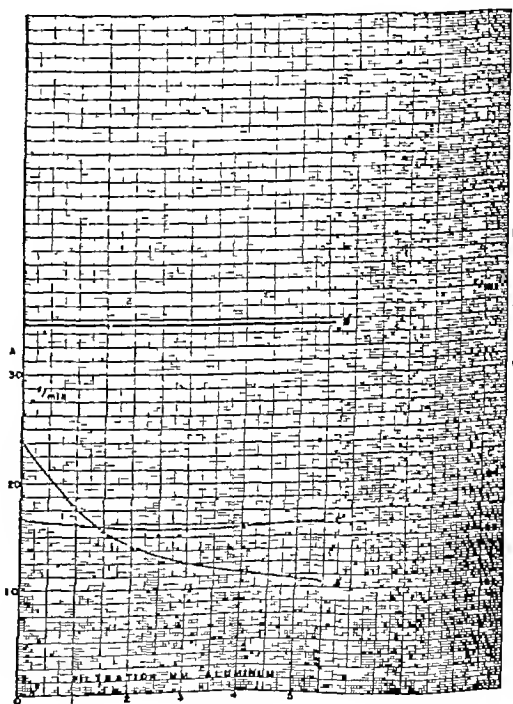


FIGURE 5A Data from Figure 5. Curves A' and C' Normalized to Maintain a Constant Dosage Rate (Intensity in r per Minute) at B (the Phantom Top or Fluoroscopic Screen) for All Values of Filter Thickness (Normal Screen Intensity Is Taken at the Value for 85 kvp, 5 ma with 1.5-mm Aluminum Filtration)

A' = patient's skin-dosage rate (with back scatter)
 C' = side-scatter intensity (phantom and field centers coincide)

optimal so far as *quality* is concerned. Therefore, taking all data into consideration, it seems fair to conclude that filtration by 3 mm of aluminum definitely increases protection of the patient, but that more than 3 mm adds little to the safety factor for either the patient or the roentgenologist.

important to point out the significance of certain of these observations in such a way that any person employing fluoroscopy can understand it

In the diagnostic range, between 50 and 140 k_vp, the quality of scattered radiation, formerly thought to be "soft," is now shown to be quite "hard." Consequently, the roentgenologist must protect himself and his associates from all of it so far as possible, and must regard all scattered radiation as sufficiently penetrating to reach the bone marrow

Present evidence (Fig 4) indicates that during fluoroscopy the patient can serve as a filter, and he should be used intelligently as such. It must be remembered that although the patient receives a large amount of radiation at any one examination, the roentgenologist over a long period of active practice — for example, thirty years — receives an enormously larger total dose. For this reason,

In addition, data derived from Figure 4 show that the spot film and fluoroscopic field size should be kept as small as possible, because, with a square field centered on the patient's mid-line, the examiner receives scattered radiation in amounts proportional to the square of the size of the field. Obviously

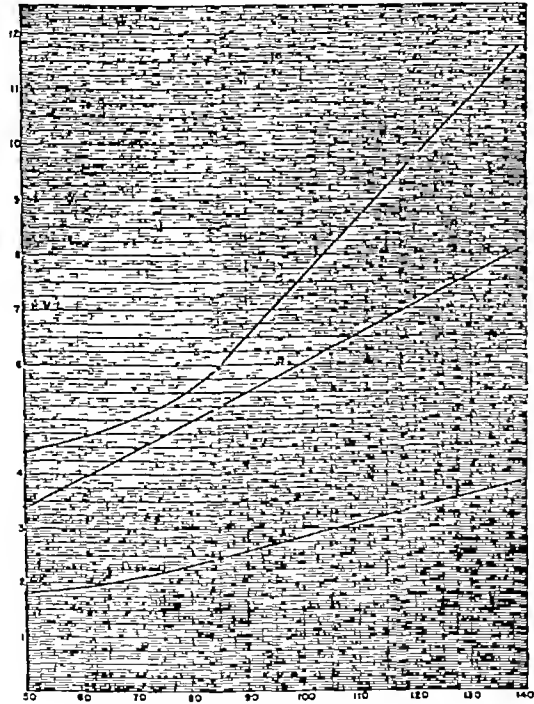


FIGURE 9 Effect of Increasing Kilovoltage on the Half-Value Layer (hvl) 5-ma, 1.5-mm Aluminum Filtration
A = table top (without back scatter)
B = phantom top
C' = side scatter (phantom and field centers coincide) Note the high hvl values at 70 kvp

the fluoroscopic beam should be centered on the patient as far distant as possible from the examiner and his aides. Although this might be regarded as a crude means of self-protection it at least reduces the intensity, even though it does not change significantly the quality of the side scatter

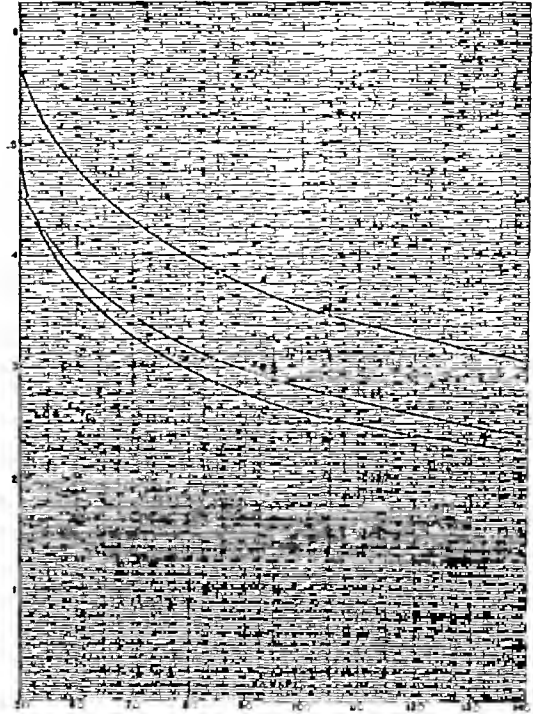


FIGURE 10 Effect of Increasing Kilovoltage on Quality, as Measured by Film Badges 5-ma, 1.5-mm Aluminum Filtration
A = table top (without back scatter)
B = phantom top
C' = side scatter (phantom and field centers coincide) Compare with Figure 9

careless technic in this respect can quickly result in a high degree of exposure

From the data shown in Figures 8 to 10, it is clear that one should not increase the kilovoltage to the range between 100 and 130 merely to increase the illumination of the screen. If the intensity on the screen is kept constant (Fig 8A), there may be certain advantages in increasing the kilovoltage. Nevertheless, it is imperative at all times to use as low a milliamperage as is compatible with proper visualization. However, the relation of kilovoltage and screen brightness requires further investigation with carefully controlled studies of the amount of radiation the patient receives, as well as the intensity and quality of the scatter

It may appear that the foregoing applies only to the roentgenologist and those assisting or observing with him, but analysis of the evidence reveals that nearly everything applicable to personnel ap-

well over 140 kvp. Furthermore, the rapid increase from 85 to 105 kvp of the side-scatter hvl (5.9 to 8.1 mm) must be taken into account when the optimal kilovoltage value is considered. From the foregoing, it appears that this value lies much nearer to 85 kvp than to 105 kvp. In any event, both side-scatter and direct-beam radiations filtered by the

employed. Empirical equations derived from the curves in Figures 9 and 10 are

$$A = \log D_s/D_i - 0.165 = \frac{0.53}{\text{hvl}}$$

$$B = \log D_s/D_i - 0.115 = \frac{0.995}{\text{hvl}}$$

$$C' = \log D_s/D_i - 0.168 = \frac{0.700}{\text{hvl}}$$

For monitoring purposes calibrations of film badges are made with 90° side scatter (C'). Since $\log D_s/D_i$ and $1/\text{hvl}$ are linear above 85 kvp, film badges must be exposed at two kilovoltages (85,

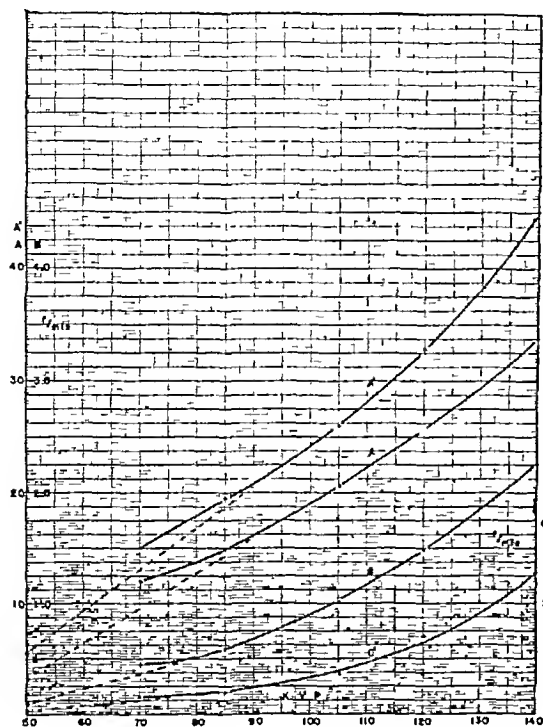


FIGURE 8 Effect of Increasing the Kilovoltage on the Dosage Rate (Intensity in r per Minute) 5-ma, 1.5-mm Aluminum Filtration

A = table top (without back scatter)
A' = patient's skin-dosage rate (with back scatter)
B = phantom top
C' = Side scatter (phantom and field centers coincide) Note the high intensity values at 70 kvp

patient have a "hard" quality and are capable of penetrating to the examiner's blood-forming organs

Summarizing and interpreting all data obtained thus far, it appears that the optimal factors for fluoroscopic procedures are a kvp of approximately 85, for this voltage and 5 ma, a tube filtration of 3 mm of aluminum

RELATION OF $\log D_s/D_i$ TO THE HALF-VALUE LAYER (HVL)

It can be shown from the data that $\log D_s/D_i$ is a reciprocal function of the corresponding half-value layer—that is, within the range 70 to 140 kvp for A and B, and within the range 85 to 140 kvp for C'. In all cases constants are involved, and these constants differ with each film emulsion em-

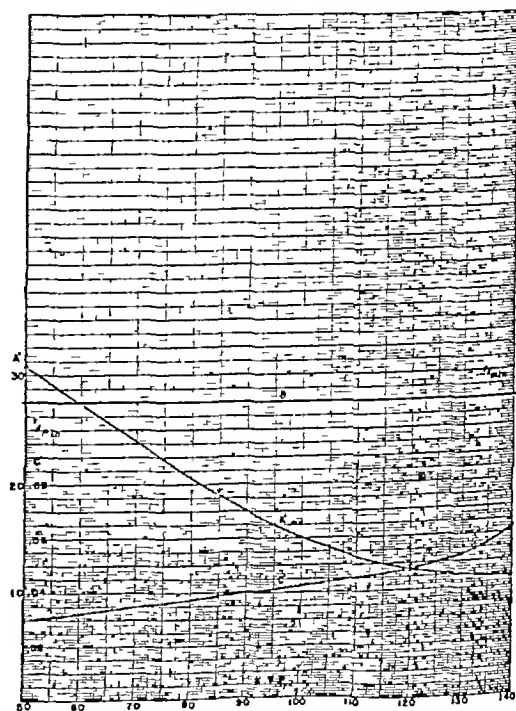


FIGURE 8A Same Data as those in Figure 8. Curves A' and C' Normalized to Maintain a Constant Dosage Rate (Intensity in r per Minute) at B (the Phantom Top or Fluoroscopic Screen), for All Values of Kilovoltage (Normal Screen Intensity Is Taken at the Value for 85 kvp, 5 ma with 1.5-mm Aluminum Filtration)

A' = patient's skin-dosage rate (with back scatter)
C' = side-scatter intensity (phantom and field centers coincide) Note the high intensity values at 70 kvp

and 105 or 120), in order to establish the constants noted above

SIGNIFICANCE OF THE PHYSICAL DATA

The material presented consists almost entirely of physical measurements. Admittedly such data are, at times, difficult for the roentgenologist, and often well-nigh impossible for the physician untrained in radiology, to interpret. It therefore seems

exposure to such a degree that occasional blood examinations can eventually be substituted for those now done twice a month

SUMMARY

A film badge that measures the quantity and quality of scattered radiation is described

Physical studies show that scattered radiation in the kilovoltage range between 50 and 140 has a "harder" quality than the direct beam that produces it.

The significance and the importance of these physical data to the roentgenologist are discussed

A radiation monitoring program is outlined, and some early results are commented upon

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INFARCTION OF THE INTERVENTRICULAR SEPTUM*

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THE electrocardiographic findings resulting from infarction of the interventricular septum were recently described by Roesler and Dressler‡ These investigators found that when the septum was involved so extensively as to include segments of both the anterior and posterior myocardial walls a characteristic electrocardiogram was regularly obtained This consisted of a posterior-myocardial-infarction pattern in the standard limb leads and an antero-septal picture in the leads from the precordium Interest in this condition led to a review of clinical and pathological material at the Veterans Administration Hospital in West Roxbury, Massachusetts

Over a period of twenty-seven months, from May, 1946, to August, 1948, there were 100 cases of acute cardiac accidents due to coronary-artery disease This group includes acute coronary thrombosis with and without myocardial infarction, myocardial infarction without demonstrable acute coronary occlusion and cases of atypical complaints and findings in which autopsy demonstrated recent myocardial infarction There were 25 deaths Autopsies were performed in 20 cases Of the anatomically examined group extensive infarction of the inter-

ventricular septum was observed in 11 Without exception there was considerable coincident involvement of the anterior or posterior walls of the left ventricle or both The papillary muscles were often infarcted

The pertinent data in this group of 11 patients with infarction of the interventricular septum are summarized in Table I

There were no women in this series because admissions at the West Roxbury Hospital are limited to men The ages varied from forty-seven to eighty, with a mean of sixty-one and three-tenths years History or physical findings of previous myocardial infarction, or both, were present in 6 patients, 2 of these also had angina pectoris Angina pectoris without a history of myocardial infarction was present in 4 cases One patient who had neither angina nor myocardial infarction had previously been studied for chronic pulmonary disease during which time there were no cardiac complaints or electrocardiographic abnormalities One patient had evidence of a gastric neoplasm and severe anemia In all but 1 patient there was clinical evidence of severe myocardial disease on admission There were signs of right-sided heart failure in 6, left-sided failure in 7, gallop rhythm in 3, embryocardia in 3 and extremely low blood pressure in 2 cases

Two of the patients had white-cell counts of over 20,000 (24,000 and 24,500) There were no other

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‡Roesler, H. and Dressler, W. Electrocardiographic pattern of infarction of interventricular septum extending from anterior to posterior aspect of heart. *Am Heart J* 34:S17-S26 1947

plies to the patient as well. As shown in Figure 5, 5A, 6 and 7, an important safety factor so far as the patient is concerned is a filter of at least 3 mm of aluminum in addition to the inherent filtration of the tube. This markedly reduces the amount of radiation received by the patient and does not appreciably "harden" the quality of the side scatter.

It goes without saying that the radiologist should use adequate aprons and gloves. A fluoroscopic timer—preferably out of comfortable reach—should be utilized, and the time should be recorded for each examination. Fluoroscopy should be done rapidly. Diaphragms should be inserted in the cone of the tube to limit the field to the screen in all positions. To avoid exposing the top of the head and upper chest, the examiner's eye should be kept aligned with the center of the screen. Fluoroscopic rooms should be large in order to minimize back scatter from ceilings and walls. Properly protected equipment should be available, and it *must* be maintained in excellent condition at all times.

As a result of the observations presented here, it is quite apparent that the manufacturer has failed to provide adequate protection. The usual combination fluoroscopic-radiographic table and large (14" by 17") fluoroscopic screen is an obvious source of danger to the examiner. As provided in the ordinary spot-film device the screen increases the safety factor considerably, but only if the field is always kept well within the limits of the screen. The large screen should therefore be discontinued, and it will be, if the roentgenologist is fully aware of his exposure hazard. In addition to this, the table commonly employed today has an open Bucky slot, which transmits large amounts of scattered radiation. Some of the newer tables are enclosed in this dangerous area, but even certain of these are not enclosed on both sides *and* the bottom. An ideal combination table should be *fully* enclosed, including the portion of the Bucky slot not in actual use. If the manufacturer does not provide one in the near future, a safe, fully enclosed table with an under-table cone extending nearly to the table top should be designed for fluoroscopy only. Nevertheless, whatever future table design may be, it still behooves the radiologist to use any and all means possible that increase the protection of the patient, himself and his assistants.

MONITORING X-RAY PERSONNEL

In the Department of Radiology at the Massachusetts General Hospital, roentgenologists and other personnel subject to irradiation in diagnostic work wear film badges containing stock dental film (Du Pont No 550), while those handling radium or assigned to high-voltage therapy are given film badges carrying special sensitive film (Du Pont No 552). Male personnel wear the badge at belt level near the trouser watch pocket, and females on the anterior chest. At the end of each day the film badges

are removed from uniforms and kept together, so that all are subjected to the same temperature variations.

Every two weeks all badges are collected, the aluminum, steel and open windows are covered with lead, and the code numbers on the cadmium windows are recorded on the film beneath with 45 kvp x-ray. After the films are removed and fresh ones inserted, the film badges are promptly returned. All badges must contain films of the same emulsion lot number, otherwise, two or more sets of standards are required.

Before the films carried by personnel are developed, duplicate standards for both the stock and the special sensitive films are prepared—the latter by exposure of film badges to a calibrated radium source. When this has been done, the films worn by personnel, the film standards and unexposed blank films, are developed as has been previously described.

The film density under each window is then measured, net density and the log ratio of density beneath the aluminum and steel "windows" are calculated, and total *r* is obtained by location of the open "window" net-density value on a newly made linear graph. The resultant data are eventually recorded on the subject's record card along with the results of the blood examinations.

Examination of the blood consists in a hemoglobin determination (photoelectric-cell technic), a white-cell count and a differential count and description of the stained smear. These examinations are made every two weeks, and, so far as possible, examinations of female personnel are made *between* ovulation and menstruation. When blood samples are being obtained, each subject is questioned about recent health, with particular attention to minor infections or manifestations of allergy. Those persistently showing deviations from the normal are sent to the Staff Clinic for a complete physical examination.

While it is entirely too soon to attempt a correlation of blood changes and radiation exposure, certain observations on monitoring are of interest. In the first place, practically all the personnel in diagnostic work are now receiving less than 0.1 r over a two weeks' period, whereas personnel handling radium are showing a greater exposure, but so far less than 0.3 r in the same period. Secondly, the developed films clearly reveal individual carelessness when it occurs. The absence of film fogging on personnel in known hazardous positions is evidence of failure to wear the film badge, and sharp shadows of the metal "windows" characterize exposure to a direct beam.

Although the monitoring has only been in effect since September, 1948, most personnel have shown progressively lower exposures. Should this happy trend continue, it may well be that the psychologic effect of having to wear a film badge will reduce

exposure to such a degree that occasional blood examinations can eventually be substituted for those now done twice a month

SUMMARY

A film badge that measures the quantity and quality of scattered radiation is described

Physical studies show that scattered radiation in the kilovoltage range between 50 and 140 has a "harder" quality than the direct beam that produces it

The significance and the importance of these physical data to the roentgenologist are discussed

A radiation monitoring program is outlined, and some early results are commented upon

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INFARCTION OF THE INTERVENTRICULAR SEPTUM*

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WEST ROXBURY, MASSACHUSETTS

THE electrocardiographic findings resulting from infarction of the interventricular septum were recently described by Roesler and Dressler‡. These investigators found that when the septum was involved so extensively as to include segments of both the anterior and posterior myocardial walls a characteristic electrocardiogram was regularly obtained. This consisted of a posterior-myocardial-infarction pattern in the standard limb leads and an antero-septal picture in the leads from the precordium. Interest in this condition led to a review of clinical and pathological material at the Veterans Administration Hospital in West Roxbury, Massachusetts.

Over a period of twenty-seven months, from May, 1946, to August, 1948, there were 100 cases of acute cardiac accidents due to coronary-artery disease. This group includes acute coronary thrombosis with and without myocardial infarction, myocardial infarction without demonstrable acute coronary occlusion and cases of atypical complaints and findings in which autopsy demonstrated recent myocardial infarction. There were 25 deaths. Autopsies were performed in 20 cases. Of the anatomically examined group extensive infarction of the inter-

ventricular septum was observed in 11. Without exception there was considerable coincident involvement of the anterior or posterior walls of the left ventricle or both. The papillary muscles were often infarcted.

The pertinent data in this group of 11 patients with infarction of the interventricular septum are summarized in Table 1.

There were no women in this series because admissions at the West Roxbury Hospital are limited to men. The ages varied from forty-seven to eighty, with a mean of sixty-one and three-tenths years. History or physical findings of previous myocardial infarction or both, were present in 6 patients, 2 of these also had angina pectoris. Angina pectoris without a history of myocardial infarction was present in 4 cases. One patient who had neither angina nor myocardial infarction had previously been studied for chronic pulmonary disease during which time there were no cardiac complaints or electrocardiographic abnormalities. One patient had evidence of a gastric neoplasm and severe anemia. In all but 1 patient there was clinical evidence of severe myocardial disease on admission. There were signs of right-sided heart failure in 6, left-sided failure in 7, gallop rhythm in 3, embrocardia in 3 and extremely low blood pressure in 2 cases.

Two of the patients had white-cell counts of over 20,000 (24,000 and 24,500). There were no other

*From the Medical Service, Veterans Administration Hospital. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

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‡Roesler H., and Dressler W. Electrocardiographic pattern of infarction of interventricular septum extending from anterior to posterior aspect of heart. *Am Heart J* 34:517-526 1947.

striking elevations of the white-cell count or erythrocyte sedimentation rates and no temperatures above 102°F

The clinical courses varied. With 2 exceptions the patients were desperately ill throughout much of their hospital courses. Two of these, however, had improved considerably and were expected to

levels during the period of bradycardia. When the block had cleared and the pulse increased the blood pressure promptly resumed its former levels.

All the 11 cases anatomically examined had coronary-artery sclerosis (Fig 1). In 2, however, there was no evidence of recent coronary occlusion. One with cancer of the stomach and severe anemia had

TABLE 1 *Data in 11 Cases of Infarction of the Interventricular Septum*

CASE No.	AGE	PERTINENT HISTORY	PHYSICAL FINDINGS	SIGNIFICANT LABORATORY FINDINGS	COURSE OF ILLNESS
1	57	Angina and hypertension for 1 yr. ankle edema for 5 days. pain 4 hr before entry	Cardiac enlargement, basal rales and ankle edema. blood pressure of 150/90	Abnormal urine. hemoglobin of 8.7 gm. sedimentation rate of 38 mm per hr. white-cell count of 10,300	Persistent angina with little or no effort. episodes of left failure. patient died suddenly and unexpectedly
2	53	Angina for 15 yr. dyspnea and edema for 3 yr. persistent pain for 12 hr	Cardiac enlargement, pitting edema	White-cell count of 19,600. sedimentation rate of 49 mm per hr	Pain returned on 6th day. angina on little or no effort. patient died suddenly and unexpectedly on 60th day
3	60	Hypertension and aortic stenosis for 7 yr. angina, dyspnea and edema for 2 yr. persistent pain for 2 days	Venous distention, enlarged heart, gallop rhythm, aortic murmur, rales and edema	White-cell count of 24,000. hemoglobin of 8 gm. blood sugar of 207 mg per 100 cc.	Persistent retrosternal pain. blood pressure of 90/80. return of pain 2 hr before death on the 6th day
4	57	Coronary thrombosis 7 yr. earlier. hypertension. persistent pain for 13 hr	Cardiac enlargement, slight cyanosis, embryocardia, gallop rhythm	White-cell count of 17,500. abnormal urine	Friction rub on 2nd day. bundle-branch block and then auriculoventricular dissociation with blood pressure of 90/70. temperature elevated to 102°F. patient died on 2nd hospital day
5	53	Heart attack 1 yr. before. angina for 6 wk. persistent pain for 12 hr	Cardiac enlargement, embryocardia, basal rales. blood pressure 74/48	White cell count of 24,000. sedimentation rate of 48 mm per hr	Temperature elevated to 102°F. severe chest pain recurred on 14th day. patient apparently recovering when he died suddenly on 18th hospital day
6		Gastric cancer. angina pectoris and ankle edema for 4 mo	Gallop rhythm, systolic basal murmur, blood pressure of 110/50. abdominal mass.	Hemoglobin of 4.3 gm. red cell count of 1,500,000	Persistent angina, decubitus, slight improvement with transfusion. gradual downhill course
7	47	Acute coronary incidents on 3 occasions. angina and dyspnea for 4 yr. recent total incapacity	Marked venous engorgement, cardiac enlargement, basal rales, pedal edema	Laboratory evidence of cirrhosis of liver	Repeated pulmonary embolism and infarction in spite of low prothrombin values. death after venous ligation
8	70	Hypertension, cardiovascular accident 2 yr. before, marked dyspnea for 4 days, crushing pain for 2 days	Venous distention, cardiac enlargement, pulmonary edema, cyanosis, friction rub	White cell count of 14,000. sedimentation rate of 36 mm per hr. abnormal urine	Transient auricular fibrillation, thrombophlebitis. patient died suddenly of cardiac rupture
9	80	Hypertensive heart disease, leg amputation for arteriosclerosis. pain for 12 hr	Cardiac enlargement, duplicated heart sounds, aortic systolic and diastolic murmurs	White cell count of 10,200. sedimentation rate of 34 mm per hr	Apparently good progress for 2 wk. one episode of transient collapse. patient died suddenly on 14th day while talking
10	56	Angina for 1 yr. congestive failure on 3 occasions. striking acute dyspnea for 24 hr	Cardiac enlargement, cyanosis and venous and hepatic engorgement, edema, blood pressure of 100/76	—	Thrombophlebitis and pulmonary infarctions. no response to therapy. gradual downhill course
11	60	Chronic pulmonary fibrosis, tearing precordial pain on and off for 4 days	Heart sounds distant, basal rales, blood pressure of 110/80	White cell count of 16,800. sedimentation rate of 36 mm. per hr. abnormal urine. nonprotein nitrogen of 55 mg per 100 cc.	Bundle-branch block followed by 3° auriculoventricular block with resultant drop in blood pressure to 50/40. patient apparently recovering when he died suddenly on 9th hospital day

recover. These and 2 who at no time appeared dangerously ill were among 5 patients who died suddenly and unexpectedly.

Auricular fibrillation was observed in 2 patients, appearing as a transient phenomenon in 1. Complete auriculoventricular block was seen in 2 cases. In 1 of these the blood pressure dropped to shock

only moderate sclerosis and narrowing, which was largely confined to the left anterior descending artery. Six showed fresh occlusions of the left anterior descending coronary artery, of these, 3 had associated involvement of the left circumflex branch, and 3 had older involvement of the right coronary artery. Three patients had fresh thrombosis of the

right coronary artery, and in each case older disease of the left anterior descending artery was present

The right ventricular side of the septum showed infarction in 3 of 11 cases studied and then only together with more extensive disease of the left side. In most cases from a third to a half (generally

The electrocardiographic pattern described by Roesler and Dressler was observed in 4 of the 11 patients, in 1 there was coincident right-bundle-branch block. In 2 the electrocardiogram was that of uncomplicated posterior myocardial infarction (Fig 2 and 3). Curiously, these were the only 2

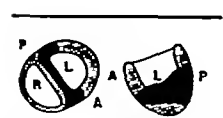
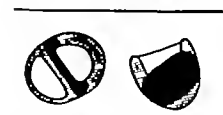
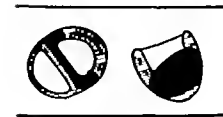







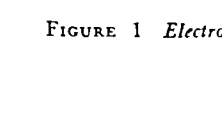
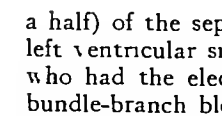
	CASE No	EXTENT OF MYOCARDIAL INFARCTION	CORONARY VESSELS INVOLVED	ELECTROCARDIOGRAPHIC FINDINGS
	1	Lower third of left half of interventricular septum with contiguous segments of anterior and posterior walls to epicardial surfaces	Acute occlusion right coronary artery; older occlusion left anterior descending artery	Posterior infarction pattern in limb leads; antero-septal in pre-cordial leads; QRS complex 0.12 sec.
	2	Lower half of left half of interventricular septum with contiguous segments anterior and posterior left ventricular walls to epicardial surfaces	Acute occlusion right coronary artery; older occlusion left anterior descending artery	Posterior-infarction pattern in limb leads; antero-septal in pre-cordial leads; QRS complex 0.12 sec.
	3	Lower half of left half of interventricular septum with contiguous segments anterior and posterior left ventricular walls to epicardial surfaces	Extensive coronary sclerosis but no new or complete occlusion	Posterior infarction pattern in limb leads; antero-septal in pre-cordial leads; QRS complex 0.12 sec.
	4	Lower two thirds of left half of interventricular septum with large contiguous segments anterior and posterior left ventricular walls to epicardial surfaces; small isolated infarction left lateral wall	Acute occlusion left anterior descending artery; older occlusion right coronary and left circumflex arteries	Electrocardiographic pattern as above followed by right bundle-branch block and later 3° auriculo-ventricular block
	5	Lower posterior two thirds entire thickness of interventricular septum with large segment posterior left ventricular wall extending to but not including anterior myocardial wall	Acute occlusion right coronary artery; older occlusion left anterior descending artery	Pattern of posterior myocardial infarction; QRS complex 0.09 sec.
	6	Lower posterior three fourths entire thickness of interventricular septum with large contiguous segments of posterior left ventricular wall extending to but not including anterior myocardial wall	Minimal coronary sclerosis; no coronary occlusion	Pattern of posterior myocardial infarction; QRS complex 0.09 sec.
	7	Patchy infarction; lower half of left third of interventricular septum extending to anterior epicardial surface at apex; large area of sub-endocardial infarction lateral wall	Acute occlusion left anterior descending artery to left circumflex artery; old occlusion right coronary artery	Left bundle branch block
	8	Anterior lower half of left half of interventricular septum not including posterior left ventricular wall; entire contiguous anterior and lateral left ventricular wall with perforation laterally	Acute occlusion left anterior descending and left circumflex arteries	Left bundle branch block; auricular fibrillation
	9	Almost entire left half of interventricular septum and adjacent large segment of anterior wall of left ventricle; no posterior involvement	Acute occlusion left anterior descending artery; old occlusion right coronary artery	Left bundle-branch block
	10	Lower anterior half of left half of interventricular septum with local extension to right endocardial surface; large adjacent segment of anterior left ventricular wall	Acute occlusion left anterior descending artery; older occlusion left circumflex artery	Left bundle branch block; auricular fibrillation
	11	Lower anterior two thirds of left half of interventricular septum with large adjacent segment of anterior myocardial wall to epicardial surface; no posterior-wall disease	Acute occlusion left anterior descending artery; marked narrowing right coronary artery	Right bundle branch block; 3° auriculoventricular block

FIGURE 1 Electrocardiographic Findings, Vessels Involved and Extent of Myocardial Involvement in 11 Cases of Infarcted Interventricular Septum

a half) of the septal thickness was involved on the left ventricular side. It is of interest that patients who had the electrocardiographic picture of right-bundle-branch block demonstrated only left septal disease at autopsy. There were no septal perforations

deaths among 25 patients with the pattern of acute posterior infarction. Frank bundle-branch block was seen in 6 cases — 4 left and 2 right. Perhaps fortuitously, both patients with right-bundle-branch block also showed 3° auriculoventricular block, possibly as the result of bilateral bundle involve-

striking elevations of the white-cell count or erythrocyte sedimentation rates and no temperatures above 102°F

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When both anterior and posterior myocardial walls with right-bundle-branch block Complete auriculoventricular block occurred in 2 patients who

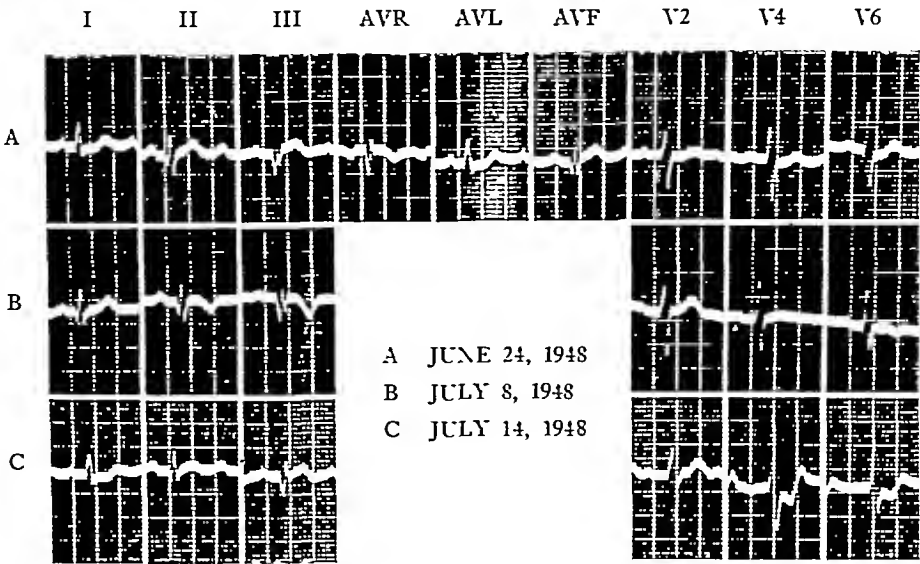


FIGURE 3 Electrocardiograms in Case 6
The findings are those of uncomplicated posterior myocardial infarction

Roesler and Dressler electrocardiographic pattern had previously shown right-bundle-branch block was observed However, bundle-branch block was The pattern of simple posterior myocardial infarction

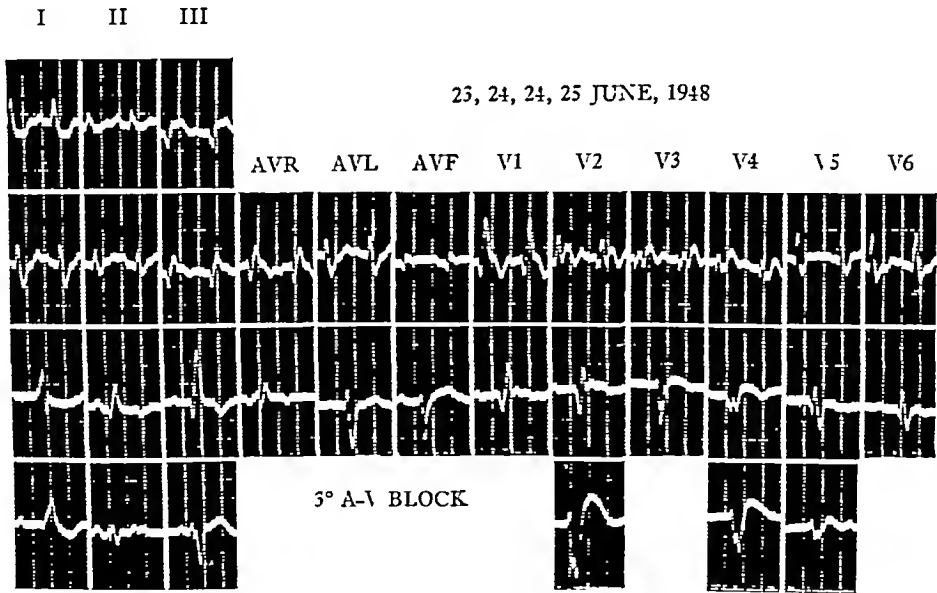


FIGURE 4 Electrocardiograms in Case 4
Note the simultaneous appearance of right-bundle-branch block and the Roesler and Dressler pattern in the second tracing This altered somewhat in the electrocardiogram obtained later the same day The last tracing was made on the day of death when 3° auriculoventricular block was present The interventricular block apparently changed from right to left-bundle-branch block This was interpreted as evidence that the idioventricular rhythm, which occurred during auriculo-ventricular dissociation, originated on the right side below the original area of block

encountered more frequently One of the patients showed the Roesler and Dressler pattern together tion was found in 2 patients who had extensive involvement of the septum

ment (Fig 4 and 5) In the 3 cases exhibiting the pattern of Roesler and Dressler without classic bundle-branch block, the QRS duration was 0.12 second Only the patients who during life showed the pattern of posterior infarction had QRS complexes of 0.10 second or less

DISCUSSION

From the data obtained in 11 fatal cases of myocardial infarction showing extensive involvement of the interventricular septum, it appears likely that the most frequent electrocardiographic phenomenon in addition to or aside from patterns of specific infarction is that of impaired interven-

trocardiographic evidence of infarction with bundle-branch block, the Roesler and Dressler pattern), the diagnosis might have been made in a total of 15 patients out of the original group of 100 There were 11 cases of myocardial infarction with bundle-branch block and 5 cases with the Roesler and Dressler pattern One patient had both Of those with bundle-branch block 3 recovered, and 7 of the 8 who died were examined post mortem Of these 6 had infarction of the interventricular septum, and 1 did not Of 5 patients exhibiting the pattern of Roesler and Dressler, 1 recovered Those who died all had involvement of the septum The patient who had bundle-branch block and the Roesler and Dressler pattern had septal infarction at autopsy

It is apparent from the patient who had myocardial infarction with bundle-branch block but no anatomic involvement of the septum that not all persons exhibiting this picture have infarction of the septum Similarly, as indicated by 2 patients who had septal infarction with electrocardiographic manifestations of uncomplicated posterior-wall involvement, infarction of the septum may occur without specific diagnostic evidence

It is therefore impossible to determine the exact incidence or mortality of extensive infarction of the interventricular septum It is likely, however, that the mortality is about 70 per cent or between two and three times that of the entire group

It is not clear whether the high mortality is the result merely of extensive myocardial destruction or whether it is a special manifestation of septal disease There is some evidence that the interference with conduction and the related tendency to arrhythmias noted in infarction of the septum materially diminished the chances of recovery The large incidence of septal infarction in this group of fatal cases is also difficult to assess It may be related to the demonstrated high mortality in septal diseases On the other hand, septal injury frequently occurs in patients with widespread or fatal coronary-artery disease

SUMMARY

Out of a group of 100 cases of acute coronary-artery disease 25 patients died, and 20 were examined post mortem Of these 11 demonstrated extensive infarction of the interventricular septum

The mortality of septal infarction could not be accurately determined but is considered to be approximately 70 per cent

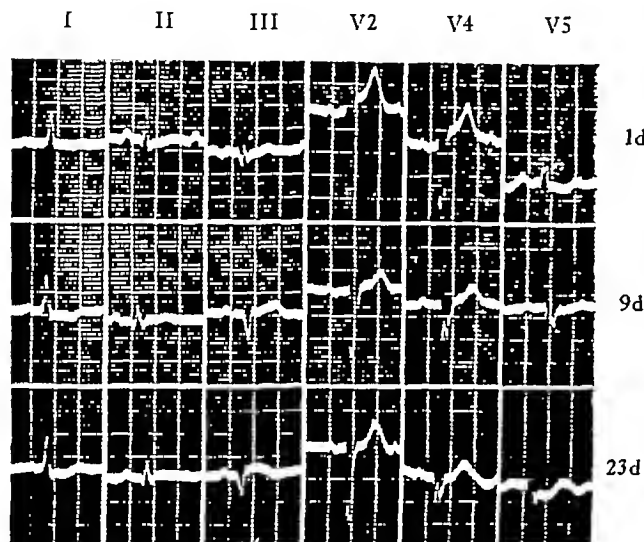


FIGURE 2 Electrocardiograms Obtained in Case 1

There is evidence of posterior myocardial infarction in the limb leads and of anteroseptal infarction in the precordial leads (The Roesler and Dressler pattern)

tricular conduction or frank bundle-branch block Less commonly, the Roesler and Dressler pattern is noted, and still less frequently the picture of uncomplicated myocardial infarction In this series the pattern of simple infarction was always that of the posterior wall — no infarction of the anterior myocardial wall was seen Patients who anatomically had extensive involvement of the anterior wall together with septal disease invariably showed bundle-branch block Atriculoventricular dissociation, a condition rarely seen in myocardial infarction, was encountered twice in this group

If one can accept these findings as criteria of interventricular-septum infarction (clinical or elec-

FATAL JARISH-HERXHEIMER REACTION WITH SUDDEN ANEURYSMAL DILATATION AND COMPLETE BRONCHIAL OCCLUSION FOLLOWING PENICILLIN THERAPY*

WILLIAM C L DIEFENBACH, M D †

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IN 1895 Jarish¹ observed after treatment with mercury an accentuation of the syphilitic roseola, and in 1902 Herxheimer² described a reaction of the various syphilitic manifestations following the use of mercury. He suggested a hypersusceptibility of the treponemes to mercury and believed that the reaction was caused by endotoxins liberated upon death of the spirochetes.

The demonstration by Mahoney, Arnold and Harris³ and others that syphilitic lesions undergo rapid involution under penicillin therapy suggested the use of this drug in the treatment of cardiovascular syphilis. Various reports of therapeutic shock following the use of penicillin in late syphilis have appeared in the literature,⁴⁻⁶ and for this reason there has been considerable hesitancy on the part of cardiologists regarding its use. This uncertainty has not been shared by most syphilologists.⁷⁻¹⁰

In general, reactions to penicillin have been fewer and milder than those with any other form of treatment for syphilis to date. Nevertheless, as with any newly introduced drug, an increasing number and variety of side reactions are observed.¹¹⁻¹⁷ A fatal case following sudden aneurysmal dilatation with complete bronchial occlusion and massive collapse of the lung is presented.

CASE REPORT

J. J. (A.H. 85142), a 75-year-old, married Negro, was admitted to the Albany Hospital by ambulance on January 7, 1949, with a chief complaint of weakness and cough of 1 week's duration. The patient had enjoyed excellent health most of his life except for gonorrhea as a youth. He had worked as a tobacco auctioneer for a number of years and had subsequently worked as a janitor. There was no history of syphilis. The family history was noncontributory. The present illness had begun with curvza, followed by a cough productive of small amounts of mucoid sputum and some elevation of temperature. He was seen by a physician, who advised hospitalization.

The temperature was 102.2°F, the pulse 130, and the respirations 36. The blood pressure was 140/80 (right arm), 135/78 (left arm).

Physical examination showed a well developed but poorly nourished man who did not appear acutely ill, but was coughing frequently. External examination of the eyes was not remarkable, there was no Horner's syndrome. The pupils were equal and reacted to light and accommodation. He was edentulous, and hearing was diminished. There was increased anteroposterior diameter of the chest, with widened interspaces, and an area of dullness on the right over the fourth and fifth ribs. Bronchovesicular breath sounds and fine crackles were heard in this area. The left lung was clear. Except for tachycardia examination of the heart was within normal limits. The remainder of the physical and neurologic examination was noncontributory.

The urine was normal. Examination of the blood demonstrated a red-cell count of 4,800,000, with a hemoglobin of 13 gm., and a white-cell count of 19,400, with 85 per cent neutrophils. Blood for a Wassermann test was drawn. The fasting blood sugar was 84 mg and the nonprotein nitrogen 36 mg per 100 cc. Blood culture was negative, but subsequently *Streptococcus viridans* was isolated from the sputum. Roentgenograms of the chest showed an area of consolidation in the lower peripheral portion of the right upper lobe consistent with pneumonia. The aorta appeared to be enlarged to the left, and there were areas of calcification within it, which suggested the possibility of an aneurysm. The electrocardiogram showed left-axis deviation and evidence of myocardial damage.

The patient was given fluids intravenously on admission and 100,000 units of aqueous penicillin every 3 hours, on the following morning the temperature was normal. On the 3rd hospital day, he complained of dyspnea, and on physical examination the trachea was deviated to the left, with absent breath sounds anteriorly and posteriorly on the left side. Another roentgenogram showed some resolution of the previously described area of increased density in the middle right-lung field. Areas of increased density had developed throughout the entire left-lung field, with narrowing of the interspaces and shifting of the mediastinum to the left consistent with atelectasis. The report on the blood Wassermann reaction was + + + +. The clinical impression was that the patient had a syphilitic aneurysm and that a Jarish-Herxheimer reaction had occurred after the penicillin therapy of pneumonia, with sudden dilatation and complete occlusion of the left main bronchus and massive collapse of the left lung.

On the following day bronchoscopic examination disclosed, about 5 cm. above the carina, a large bulge in the posterior wall of the trachea, which was pulsating in a marked fashion. The bronchoscope could be introduced beyond this point and the carina was then identified, but the left bronchus was found to be completely occluded by an extrabronchial mass intruding upon the bronchial lumen. It was impossible to introduce the bronchoscope into the left bronchus, the right being completely normal. Subsequently a titer of 120 was obtained in the complement-fixation test for syphilis, and a spinal-fluid Wassermann test was + + + +.

The patient went progressively downhill, with a daily temperature elevation to 103°F, and died on the 58th hospital day with no essential change in the previously described physical findings.

Autopsy showed collapse of the left lung. The heart was not unusual, weighing 280 gm. There was a large saccular aneurysm of the arch and descending aorta, which measured about 10 cm. in diameter. The aneurysm, which was occluding the left main bronchus and compressing the lower 4 or 5 cm. of the trachea, was thin walled and contained a large rubbery clot that was loosely adherent. The bodies of the fourth and fifth dorsal vertebrae were eroded to a depth of 2.5 cm., and the intervertebral disks between them were normal.

DISCUSSION

The unpredictable Jarish-Herxheimer reaction, or so-called therapeutic shock, occurs after the first injection of an antisyphilitic drug. There is a local response at the injection site, a general response of fever and malaise and a focal exacerbation of symptoms. The focal response is the one of concern and principally so in tertiary syphilis, for its occurrence in over 50 per cent of patients with early syphilis treated with penicillin is not of conse-

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Two patients had no acute coronary occlusion. Six had acute thrombosis of the left anterior descending coronary artery. Similarly, patients with

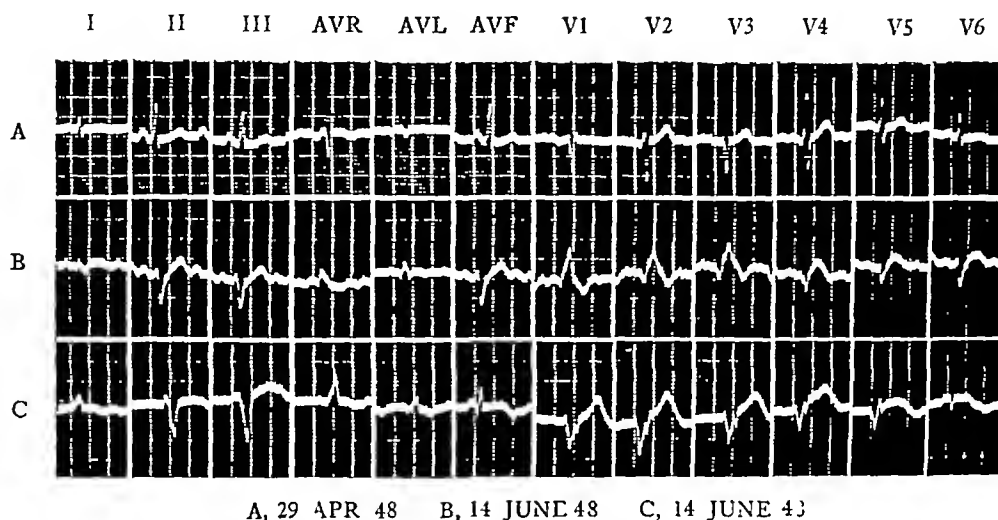


FIGURE 5 Electrocardiograms in Case 11

The first tracing was obtained during an earlier hospitalization. The second electrocardiogram, made during the first day of the last illness, showed evidence of right-bundle-branch block and anterior myocardial infarction. In the last tracing there was an apparent change from right to left-bundle-branch block during a period of 3° auriculoventricular block and dissociation.

scending branch of the left coronary artery, and 3 showed primary acute involvement of the right coronary artery. Those with disease of the right

acute thrombosis of the left anterior descending artery also had old occlusion of the right coronary or the left circumflex artery.

FATAL JARISH-HERXHEIMER REACTION WITH SUDDEN ANEURYSMAL DILATATION AND COMPLETE BRONCHIAL OCCLUSION FOLLOWING PENICILLIN THERAPY*

WILLIAM C L DIEFENBACH, M D †

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IN 1895 Jarish¹ observed after treatment with mercury an accentuation of the syphilitic roseola, and in 1902 Herxheimer² described a reaction of the various syphilitic manifestations following the use of mercury. He suggested a hypersusceptibility of the treponemes to mercury and believed that the reaction was caused by endotoxins liberated upon death of the spirochetes.

The demonstration by Mahoney, Arnold and Harris³ and others that syphilitic lesions undergo rapid involution under penicillin therapy suggested the use of this drug in the treatment of cardiovascular syphilis. Various reports of therapeutic shock following the use of penicillin in late syphilis have appeared in the literature,⁴⁻⁶ and for this reason there has been considerable hesitancy on the part of cardiologists regarding its use. This uncertainty has not been shared by most syphilologists.⁷⁻¹⁰

In general, reactions to penicillin have been fewer and milder than those with any other form of treatment for syphilis to date. Nevertheless, as with any newly introduced drug, an increasing number and variety of side reactions are observed.¹¹⁻¹⁷ A fatal case following sudden aneurysmal dilatation with complete bronchial occlusion and massive collapse of the lung is presented.

CASE REPORT

J. J. (A.H. 85142), a 75-year-old, married Negro, was admitted to the Albany Hospital by ambulance on January 7, 1949, with a chief complaint of weakness and cough of 1 week's duration. The patient had enjoyed excellent health most of his life except for gonorrhea as a youth. He had worked as a tobacco auctioneer for a number of years and had subsequently worked as a janitor. There was no history of syphilis. The family history was noncontributory. The present illness had begun with coryza, followed by a cough productive of small amounts of mucoid sputum and some elevation of temperature. He was seen by a physician, who advised hospitalization.

The temperature was 102.2°F, the pulse 130, and the respirations 36. The blood pressure was 140/80 (right arm), 135/78 (left arm).

Physical examination showed a well developed but poorly nourished man who did not appear acutely ill, but was coughing frequently. External examination of the eyes was not remarkable, there was no Horner's syndrome. The pupils were equal and reacted to light and accommodation. He was edentulous, and hearing was diminished. There was increased anteroposterior diameter of the chest, with widened interspaces, and an area of dullness on the right over the fourth and fifth ribs. Bronchovesicular breath sounds and fine crepitant rales were heard in this area. The left lung was clear. Except for tachycardia examination of the heart was within normal limits. The remainder of the physical and neurologic examination was noncontributory.

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quence^{11, 16} In late syphilis it may cause a fatal reaction as in the case described above In cardiovascular syphilis the edema and swelling of the syphilitic involvement about the coronary ostia may result in sudden closure of a coronary artery, or an aortic aneurysm may rupture In laryngeal syphilis a gumma may swell and cause asphyxia The reaction is thought to be the result of the sudden death of a large number of spirochetes, with the subsequent release of proteins and toxins from the treponemes It has also been observed to occur since the introduction of penicillin into antisymphilitic therapy

Moore,⁷ in 1947, using penicillin in 50 cases of cardiovascular syphilis with aortic aneurysm or aortic insufficiency, divided them into two groups One was initially treated with 1000 units gradually increased to average therapeutic dosage, and the other with 50,000 to 100,000 units from the start In neither group did any untoward reactions or damage occur as detectable by sedimentation rates, temperature, white-cell count and so forth Moore concluded that the Herxheimer reaction need not be greatly feared There is no proof, however, that antisymphilitic therapy heals cardiovascular lesions even though it heals visible and palpable visceral lesions Untoward reactions are observed, as in the case described above, in which penicillin was given for pneumonia before it was discovered that the patient had syphilis There were no clues in the history or physical examination until the serologic report returned several days later

SUMMARY

The Jarish-Herxheimer reaction in cardiovascular syphilis is described

An unusual fatal case, in which sudden aneurysmal dilatation, with complete bronchial occlusion and massive lung collapse, followed penicillin therapy for pneumonia, is reported

The suggestion is made that some caution be exercised in the penicillin treatment of elderly patients for conditions other than syphilis

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ACUTE APPENDICITIS WITH CONCOMITANT SITUS INVERSUS

Report of a Case

WILLIAM GEORGE ABEL, III, M D * ' 1

NEW YORK CITY

SITUS inversus viscerum is uncommon, only 200 cases having been catalogued up to 1912 by Karashima¹. By 1925, approximately 160 more cases had appeared in the literature,² and in 1938 Larson³ estimated that over 475 cases had been reported. Adams and Churchill⁴ stated that situs inversus had occurred in 23 cases out of 237,112 admissions to the Massachusetts General Hospital. Sherk⁵ observed this condition in 10 cases among 347,000 hospital admissions. Willis⁶ reported 3 cases in 10,000 hospital admissions. LeWald⁷ recorded 29 cases in 40,000, and Francisco and Ongpin⁸ 36 cases in 126,000 x-ray studies. Guenther⁹ reported 3 cases in 22,000 autopsies, LeWald⁷ 1 case in 50,000 autopsies, and Francisco and Ongpin⁸ 4 cases in 10,000 autopsies. Over a forty-year period, approximately 10,000 cadavers were dissected at Columbia University College of Physicians and Surgeons, with but 1 case being discovered.²

Most writers on this subject believe that the transposed organs develop normally and that their anatomically abnormal site has no ill effect upon their usual function or upon the patient's well-being. Situs inversus appears to be twice as common in males as in females, and total transposition of the organs is far more common than partial inversion.¹⁰⁻¹⁴

HISTORICAL

Perhaps the earliest known record of situs inversus viscerum dates from the time of Aristotle, who noted transposition of organs in 2 animals.^{1, 12-14} Beck¹⁵ reports that the first recorded case in man occurred in the person of Marie de Medici, Queen of France. In 1824 the use of auscultation and percussion as diagnostic aids was first discussed by Küchenmeister.¹⁶ Vehsemeyer,¹² in 1897, was able to demonstrate this condition by means of the roentgen ray. Pol,¹³ in reviewing the literature in 1935, found 46 cases of left-sided appendicitis associated with situs inversus. Blegen,¹⁷ in 1949, records 144 cases of situs inversus, with 158 operations. He found that a diagnosis of situs inversus was made before operation in only 39 cases in which the patient was operated upon for appendicitis.

EMBRYOLOGY

Situs inversus viscerum should not be confused with failure of rotation or malrotation. In malrotation the viscera occupy their usual anatomic po-

sition, the abnormality occurring in the midgut. The midgut occupies the umbilical cord up to about the tenth week of intrauterine life when the coils of gut return to the abdomen, which has grown large enough to accommodate them. Under normal conditions the proximal jejunum leaves the cord first, passing from right to left in a counterclockwise direction, using the superior mesenteric artery as its axis. These coils are packed more and more to the left by the following loops of intestine until the cecum and ascending colon, which are the last to enter, lie in the right hypochondrium. If, however, the coils of gut return to the abdomen en masse, retaining the position occupied in the cord, the entire large intestine will be on the left side with the small intestine on the right and the terminal ileum entering the cecum from right to left. This condition is known as failure of rotation. When there has been partial rotation, the coils lying between nonrotation and their normal position, the anomaly is referred to as malrotation.^{1-4, 8, 9, 19} Many theories have been advanced in an attempt to explain the cause of situs inversus, but as yet no satisfactory, acceptable hypothesis has been advanced.

Karewski²⁰ divides the cases into congenital and acquired, and the causes into total transposition of the viscera, failure of descent of cecum, excessive length of normally located appendix and mobile cecum with adhesions binding it to the left side.

DIAGNOSIS

Situs inversus, per se, is usually diagnosed during routine physical examination and confirmed by appropriate x-ray studies or is discovered accidentally at operation. The diagnosis of appendicitis rests upon a fairly regular chain of clinical symptoms and physical signs that do not need to be discussed. The diagnosis of "left-sided" appendicitis should be suspected when there are a history of epigastric or periumbilical pain followed by nausea or vomiting, clinical finding of dextrocardia, tenderness in either lower quadrant and reversal of the stomach shown by barium swallow.

CASE REPORT

S S (B H 20503-48), a 14-year-old Italian boy, entered the hospital with the complaint of periumbilical pain. On the morning before his admission to the hospital he had experienced dull periumbilical pain which remained constant and did not radiate. He spent the day in bed and later that evening became nauseated and vomited several times. He had been anorexic since the onset of his illness. He had

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had one normal bowel movement on the day of admission. He had not received any cathartic or enema. He had no urinary or respiratory symptoms. He entered the hospital approximately 28 hours after onset of symptoms.

The past history revealed that the patient had been attending the cardiac outpatient department for many years because of "reversed heart." This had not in any way limited his physical activities.

Physical examination revealed a well developed but undernourished boy who appeared acutely ill. He seemed to be more comfortable with his thighs flexed on his trunk. His skin was hot and dry, with no rash or petechiae. Positive findings were confined to the chest and abdomen. The point of maximum cardiac impulse was in the fifth interspace 8 cm. to right of the midsternal line. Regular sinus rhythm, with sounds of good quality, was heard. The abdomen was flat and muscular, with no rigidity or spasm. There were marked tenderness and direct rebound tenderness in the left lower quadrant, but none in the right lower quadrant. There was no abdominal scar or masses. Rectal examination revealed no tenderness on the right and marked tenderness on the left.

The temperature was 103.2°F by rectum, the pulse 100, and the respirations 20. The blood pressure was 110/70.

Urinalysis was negative. Examination of the blood disclosed a white-cell count of 13,750, with 82 per cent neutrophils. A chest plate revealed dextrocardia. A barium swallow showed a situs inversus of the stomach. A preoperative diagnosis of situs inversus viscerum with acute appendicitis was made, and after restoration of fluid and electrolyte balance the patient was taken to the operating room. The abdomen was entered through a left McBurney incision, and an acutely inflamed appendix was removed. Exploration revealed marked mesenteric adenitis, ileum entering the cecum from right to left, and a left-sided liver. The patient was up and about on the morning after operation and was discharged on the 7th day completely asymptomatic.

SUMMARY

Situs inversus is uncommon. A review of the literature with some statistics pertaining to the condition is given.

The embryology of nonrotation and malrotation is discussed.

Aids in the diagnosis of situs inversus complicated by appendicitis are briefly listed.

This condition should be considered in the differential diagnosis whenever a patient complains of left-sided pain.

A report of a case is given in detail.

560 West 165th Street

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MEDICAL PROGRESS

ACTIVE IMMUNIZATION (Concluded)

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BOSTON

TETANUS

Effectiveness of Toxoid

The results of tetanus-toxoid immunization in the United States Army in World War II have been presented in illuminating detail by Long and Sartwell,¹¹⁰ whose paper has been abstracted *in extenso* in the *Journal*.¹¹¹ Long⁸ has also presented a brief summary of this material. The remarkable results obtained in the United States Army have been so well publicized that it will suffice to present here only the essential facts. The procedure employed was to administer three doses of 1 cc each, at intervals of three to four weeks, followed by a single stimulating dose of 1 cc at the end of the first year, and an emergency booster dose upon the occurrence of a wound or other injury that might result in tetanus. During the early part of the war, booster doses were also given to personnel departing for a theater of operations, unless such a dose had been administered within the preceding six months, this practice was later eliminated. All told, 12 cases of tetanus occurred in the Army during World War II, in only 4 of which the patients had received a full primary immunizing course as well as a booster dose of toxoid. The tetanus rate per 100,000 wounded and injured was 0.44 if all cases are considered and 0.22 if cases with no active immunization are excluded. These rates may be compared with those of other periods in the United States Army: for World War I, 13.4 per 100,000, and from 1920 to 1941 inclusive, 2.4 per 100,000. By contrast, the reported incidence in the Japanese Army and Navy from 1940 through 1944 was about 10 cases per 100,000 wounded. Abundant additional evidence is cited by Long and Sartwell, to substantiate the extraordinary prophylactic effectiveness of tetanus toxoid properly administered.[†]

A recent review and study by Press¹¹² has analyzed the arguments for and against the routine use of tetanus toxoid. He cites old and new data that re-emphasize the danger of contracting tetanus from trivial or unrecognized injuries. He has collected 100 clinical cases of tetanus that, when added to numerous previous reports, make a total of 982 cases in which the degree of the infecting

injury was defined. Fifteen per cent of all these cases arose from "trivial injury." Three hundred and fifty-one of the entire group could be analyzed for the presence or absence of *any* known injury, 34.5 per cent were recorded as "injury unknown." These observations lend further support to the routine use of toxoid, since the residual immunity left by periodic inoculations of toxoid should afford tangible protection even against unrecognized infection.

Limitations of Effectiveness

The duration of this residual immunity and the degree and rapidity of response to a booster dose have yet to be sufficiently defined. McBryde and Poston¹¹³ measured the persistence of antitoxin in Negro children at various intervals after administration of two doses of alum-precipitated toxoid, given two and a half months apart. Their data may be analyzed according to a generally accepted (but probably conservative) standard of protection: the presence of at least 0.1 unit of antitoxin per cubic centimeter of serum. By this standard, the following numbers of children were still protected at the indicated interval after primary inoculation: after one year, 30 out of 33, after two and a half years, 13 out of 29, and after five years, 2 out of 15.

McBryde and Poston then measured the response to booster doses of varying size, and found that at one week after a stimulating dose given at either two and a half or five years subsequent to primary immunization, a tenfold to eight-hundred-fold rise in antitoxin titers was obtained. The degree of response varied according to the size of the stimulating dose employed, but not in a simple linear proportion. For example, in the group injected two and a half years after primary inoculation, 1 cc produced an average titer of 7 units, 0.1 cc produced 3 units, and 0.004 cc produced 0.3 unit. The results after a five-year interval were closely similar.

Comparable findings in a larger group of subjects have been reported by Wishart and Jackson.¹¹⁵ They observed a sevenfold geometric mean rise in titer four weeks after a subcutaneous booster dose of 0.1 cc, and a thirty-two-fold rise after 1.0 cc of toxoid. Since 1 out of 67 subjects failed to reach a "protective" titer after receiving 0.1 cc, whereas all of 55 subjects reached or exceeded such

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†Results with alum precipitated toxoid in the United States Navy were comparable: only 2 cases of tetanus in definitely immunized personnel having occurred among 89,995 wounded in this service.¹¹²

had one normal bowel movement on the day of admission. He had not received any cathartic or enema. He had no urinary or respiratory symptoms. He entered the hospital approximately 28 hours after onset of symptoms.

The past history revealed that the patient had been attending the cardiac outpatient department for many years because of "reversed heart." This had not in any way limited his physical activities.

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evidence as was offered to show that the vaccine afforded protection was counterbalanced, in the minds of most phthisiologists and health officers by the belief that its use might prove not only useless but also hazardous. Perhaps the story would have been different had Calmette been able to afford the expense involved in adequate laboratory studies before the vaccine was employed in human beings. There is a wistful comment, in one of the papers of Calmette and Guérin²² reporting on the immunization of cattle—

It would be desirable if this method could be tried more extensively in a larger number of animals and followed during a period of years corresponding to the average life of cattle in order to define its practical value. Unfortunately, actual economic conditions oblige us to await more favorable circumstances for the purchase and the conservation of a sufficiently significant herd.

One wonders how many studies such as this have been left hanging in a state of indecision for many years because of inadequate facilities for their evaluation at the start.

Results of Controlled Studies

At all events there is now a large accumulation of controlled evidence regarding the ability of BCG to reduce the incidence of tuberculous infection. The first such studies appear to have been those of Heimbeck and his associates²³ who observed that the incidence of clinical tuberculosis in tuberculin-negative medical or nursing students was very much higher than that among those who were tuberculin-positive when first enrolled. These investigators subsequently found that the administration of BCG to the tuberculin-negative groups produced as much as a sevenfold reduction in the incidence of subsequent clinical tuberculosis as compared to the unvaccinated negative reactors. In Denmark a recent outbreak of tuberculosis in a girl's school arising from an infected teacher gave striking support to the efficacy of vaccination.²⁴ Among 105 tuberculin-positive pupils 2 cases of tuberculosis occurred during a three-year period, among 106 tuberculin-negative pupils who had been vaccinated with BCG there were 2 cases, whereas among 94 unvaccinated tuberculin-negative pupils there were 41 cases with 1 death.

On this continent, several studies have been initiated during the last twenty years with varying results. Levine, Vogel and Rosenberg²⁵ and Levine and Sackett²⁶ continued a study program begun earlier by Park et al.²⁴ The earlier series (1926-32) in which infants were vaccinated or not according to the choice of their parents had shown 0.68 per cent tuberculous deaths in 445 vaccinated infants as against 3.38 per cent in 545 controls. Strict alternation in selecting controls was applied in the second series (1933-44) the death rates then became 1.41 per cent in 566 vaccinated infants as against 1.51 per cent in 528 controls. Levine and Sackett

concluded that the favorable results of the first series had been weighted by the inevitable tendency to vaccinate children of the more intelligent and co-operative parents.

Aronson and Palmer²⁷ have reported a six-year study of BCG vaccination in 1550 tuberculin-negative North American Indians 1457 closely comparable subjects being observed as controls. Careful follow-up studies included x-ray examination, tuberculin tests, histories of exposure to tuberculosis (21.4 per cent in those vaccinated and 19.8 per cent in the controls) and determination of the cause of death when ascertainable. Among the vaccinated subjects 40 cases and 4 deaths from tuberculosis occurred, compared to 185 cases and 28 deaths in the controls. Thus vaccination appeared to exert a fourfold protection against the disease and a sevenfold protection against death from tuberculosis.

Rosenthal and his associates²⁸ have completed a ten-year study of 1417 normal newborn infants given BCG vaccine, compared with 1414 controls. Eleven and 39 cases of tuberculosis respectively, developed—more than a threefold protection rate. Among infants definitely exposed to tuberculosis, there was 1 case in 98 vaccinated subjects against 4 cases among 63 random controls subject to comparable exposure.

Ferguson²⁹ undertook to control with BCG the alarmingly high incidence of tuberculosis in student nurses in Saskatchewan. Because of the urgent situation and the encouraging reports of BCG vaccination from Scandinavia it was decided not to maintain an unvaccinated control group; therefore the incidence of tuberculosis in tuberculin-negative nurses vaccinated from 1939 to 1943 was compared to that in similar unvaccinated groups observed from 1934 to 1938. The incidence of tuberculosis was 4.27 times higher in the unvaccinated nurses in general hospitals and 5.03 times higher in sanatorium nurses compared to the corresponding vaccinated groups. More recently Ferguson and Simes³⁰ have reported the results of a twelve-year study in 506 vaccinated and 503 unvaccinated Indian infants. 73 per cent of all subjects in the study were in families including both vaccinated infants and controls. Six cases of tuberculosis and 2 deaths from tuberculosis occurred in the vaccinated group as against 29 cases and 9 deaths in the controls—a protection rate of 4.81 against disease and 4.51 against death.

In general the studies cited above have led to a growing belief well established in parts of continental Europe but recent in this country, that BCG can be a valuable agent in the control of tuberculosis.³¹ Meanwhile, the studies referred to have been thoroughly combed for flaws by various authorities in the field. It has been pointed out that, in Levine's series the infant patients were not separated from their tuberculous environment pending the development of post-vaccinal immunity;

titers after receiving 10 cc, the authors suggest that the smaller dose is inadequate as a routine booster. It should be noted here that McBryde and Poston found that 0.1 cc, given intradermally five years after initial immunization, produced a response at least as good as that obtained with 10 cc subcutaneously. This supports the frequent observation of other workers with various antigens^{11 145 146} that a stimulating dose is highly effective when administered by the intradermal route.

Long and Sartwell¹¹⁰ likewise demonstrated the long persistence both of antitoxin levels and of the capacity to respond rapidly and adequately to a booster dose. Of 8 subjects tested four or five years after primary injections, all possessed 0.01 unit per cubic centimeter or more, 2 had titers of 1.0 to 5.0 units. One week after injection of the stimulating dose, 7 were tested again, and all were above 0.5 unit, 4 having titers of 5 to 20 units.

Thus, it appears to be fairly well established that detectable—and as a rule significantly high—titers of antitoxin persist for at least four or five years after primary immunization, and that a striking increase in titer will appear within a week of a booster injection. But cases of tetanus sometimes reach a fatal outcome in less than a week, so that the question arises, How soon will the titer begin to rise after injection of an emergency booster dose? Gold³¹⁶ has reported titrations on the fourth to the seventh day inclusive after booster doses in from 8 to 20 subjects. The first hint of a response was seen (in 1 subject out of 8) on the fourth day. A recent observation on 5 subjects titrated from the fourth to the tenth day inclusive³¹⁷ confirms these findings, and suggests that the response is at or near its maximum by the tenth day. Miller and his associates³¹⁸ have followed the initial response to a booster dose in about 100 subjects, finding that the best sequence (basic immunization with adsorbed toxoid, booster with fluid) induces a rise in most subjects by the fourth day and in all by the fifth day. Thus, it appears that in the presence of a low antitoxin titer a booster dose given immediately after injury may not always induce a response with sufficient speed to combat a fulminating tetanus infection, such as can occur when contaminated material is driven directly into the central nervous system. One is led therefore to the conclusion that optimum protection against tetanus may best be achieved by application of the following principles: adequate primary immunization, administration of periodic maintenance doses of toxoid, perhaps at intervals of approximately 4 years, administration of a booster dose after such injuries as may result in tetanus, and consideration of the prophylactic administration of antitoxin if such an injury has occurred within the meninges. A good description of a well planned and well organized industrial program of anti-tetanus immunization³¹⁹ and an excellent summary

of the principles and applications of reimmunization with tetanus toxoid³²⁰ have recently appeared and will be helpful to any physician planning the use of toxoid in individual patients or in groups.

Reactions

Wishart and Jackson³¹⁵ report the occurrence of severe local reactions in 4.7 per cent of their subjects receiving 10 cc as a booster dose. Although this frequency is not serious, they believe that it deserves to be reduced if possible, and state that preliminary trials have shown that refinement of the antigen may largely circumvent this problem. Pillemer and his associates^{321 322} have succeeded in preparing tetanus toxoid in a highly purified and concentrated form. This preparation has been sufficiently freed of anaphylactogenic constituents of the culture medium so that it will not cause shock in guinea pigs sensitized to the medium, the crude toxoid causing severe or fatal anaphylaxis in similarly sensitized animals. The method of purification is based upon precipitation of the toxoid substance with methyl alcohol in the cold, as has also been done by Pillemer with diphtheria toxoid.^{87 88} The successful application of such methods may make possible the distribution of toxoids that contain only the essential immunizing substance and perhaps also a stabilizing nonantigenic diluent, which will eliminate the risk of reactions to extraneous substances. The achievement of this objective may be hastened as a result of the series of studies by Mueller and his associates,^{323 325} which are directed toward the production of tetanus toxin in a medium consisting only of known chemical substances. Even when this is accomplished, however, there will remain the problem—as yet unimportant but likely to increase in frequency as more and more booster doses of toxoid are given—of sensitization and consequent untoward reactions caused by the toxoid protein itself.

TUBERCULOSIS

Attempts to prepare a vaccine against tuberculosis began with Koch's experiments with old tuberculin. It early became apparent that no significant protection against tuberculous infection could be achieved with anything less than whole bacilli as the antigen. Although many useful and sometimes promising studies have been carried out using killed organisms in laboratory³²⁶ or field³²⁷ experiments, major interest has for some years been focused on the use of the *Bacillus Calmette-Guérin* (BCG)—a vaccine derived from living tubercle bacillus by attenuation of a virulent bovine strain through prolonged cultivation on a bile-containing medium.³²⁸ For practically a generation, BCG has been the center of controversies regarding its safety or its efficacy. Unfortunately, the early clinical trials in France were not supported by adequate comparisons with valid control groups, so that such

evidence as was offered to show that the vaccine afforded protection was counterbalanced, in the minds of most phthisiologists and health officers, by the belief that its use might prove not only useless but also hazardous. Perhaps the story would have been different had Calmette been able to afford the expense involved in adequate laboratory studies before the vaccine was employed in human beings. There is a wistful comment in one of the papers of Calmette and Guérin²⁹ reporting on the immunization of cattle

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that the diagnosis of the cause of death was not always reliable, and that the absence of morbidity data makes interpretation of the over-all results of the study unsatisfactory³⁴⁰ Furthermore, Wallgren³³¹ shows that the results, if corrected to exclude subjects who were exposed to tuberculous infection prior to vaccination, are as favorable as those of Rosenthal Tytler³⁴¹ prefers to draw no conclusions from Levine's study On the other hand, favorable reports such as that of Aronson and Palmer³³⁵ have also been subject to criticism Levine³⁴² and Wilson³⁴⁰ point out that in this study the cause of death was not always verified, the degree of exposure to tuberculosis in vaccinated subjects and controls was only "fairly well" balanced, and the intensity of exposure to contacts was not quantitatively evaluated The question is raised whether good results in American Indians "can legitimately be transferred to civilized peoples having a higher degree of genetic immunity and exposed, as a rule, to a lower risk of infection"³⁴⁰ However, this last comment comes from the same paper that concludes, from Levine and Sackett's data, that "under ordinary conditions in which the infants are brought up in a tuberculous environment (BCG) seems to confer little, if any, protection" — that is, an infant in New York City must be segregated from heavy exposure to tuberculosis until he has established immunity Either line of reasoning could be correct, but it is hard to accept both at once

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Present Programs and Policies

Nevertheless, the mass of controlled evidence supporting the efficacy of BCG vaccination, considered along with the much larger uncontrolled groups, which are too numerous to be cited here but have been well tabulated by Levine,³⁴² has led to very extensive use of the vaccine in the last few years In Norway, BCG vaccination is reported to have been made compulsory³⁴⁴ for tuberculin-negative persons in the following groups: all persons in a tuberculous environment, doctors, nurses, hospital workers and other groups with a high tuberculosis morbidity, men liable for military service, and children of school-leaving age, students and so forth A widespread voluntary immunization program is going forward in Sweden³⁴⁵ and Denmark³⁴⁶

In 1946 the United States Public Health Service undertook the sponsorship of extensive trials of BCG vaccination,^{346 347} laying out a carefully controlled program and using vaccine furnished by a single laboratory New York State has undertaken a somewhat similar program, under the direction of Birkhaug,³⁴⁸ who has for a number of years been concerned with this problem At much the same time a joint committee representing various tuberculosis-control agencies in Great Britain sponsored an appraisal of the policy to be followed in that country The comprehensive report for this committee prepared by Tytler³⁴⁹ concluded that BCG was harmless, that the weight of available evidence indicated that BCG offered definite protection against tuberculosis in groups subject to undue risk from this disease, that the best method of application of the vaccine was probably by puncture or scarification, and that the technical difficulties involved in studies of the use of BCG were such that a single, carefully controlled and supervised source of supply should be established The need for careful and continued evaluation of the vaccine through properly designed and controlled programs has been reflected in the conclusions of a second United States Public Health Service conference on the problem,³⁵⁰ in the stated policy of the American Trudeau Society³⁵¹ and in the promulgation of regulations for the use of BCG by the New York State Department of Health³⁵² The history and background of the developments in BCG vaccination that have underlain these decisions have been amply presented in recent reviews by Aronson³⁵³ and Birkhaug³⁵⁴

Complications

Thus, it may be anticipated that BCG vaccine will be employed in this country on an increasing scale. What, if any, are its dangers and limitations? First among the latter is the fact, observed in every study cited, that it does not provide 100 per cent protection. In this respect it differs from no other immunizing agent. Secondly, it does cause occasional untoward reactions. Holm³⁴⁵ observed an incidence of 0.7 per cent of abscesses or glandular suppuration among 3369 intracutaneous vaccinations. Difs³⁵⁵ has seen serious necrosis in 0.3 per cent of 6447 vaccinations, the incidence among school children running as high as 2 or 3 per cent. However, Wallgren reports that areas of reaction larger than 10 by 10 mm occur in only 2.8 per cent of subjects, he considers that the constant and growing spontaneous demand of parents in Sweden for BCG vaccination of their children is sufficient evidence that the reactions are unimportant.³⁴¹ Törnell³⁵⁶ finds that the incidence varies greatly with the physician performing the vaccination. Lomholt³⁵⁷ reports a case of lupus vulgaris developing at the site of vaccination. Various workers stress the likelihood of producing an abscess at the inoculation site if BCG is administered to a tuberculin-positive subject. On the other hand, Wallgren,³⁵⁸ from an extensive experience, states that there is no danger in vaccinating already infected persons, and Nègre and Bretey,³⁵⁹ in reviewing this field, find that focal and general reactions are induced in tuberculous patients only by injection of very large doses of BCG (1 mg) compared to the usual immunizing dose of 0.05 to 0.1 mg.

Technic of Vaccination and Vaccine Preparation

A decade ago Rosenthal³⁶⁰ developed the multiple-puncture technic for cutaneous BCG vaccination. This method has been employed since by others, including Birkhaug,³⁶¹ who has devised for the purpose a spring-action, multiple-point apparatus.³⁶² His experimental data³⁶¹ and certain of the available clinical data suggest that the cutaneous route induces a higher degree of immunity than intracutaneous inoculation, and it is the opinion of some that reactions are minimized with the use of the cutaneous route.^{349, 363} Its disadvantages, on the other hand, are said to be that it is in general somewhat slower in performance, the exact amount of inoculum cannot be determined, and the apparatus is difficult to sterilize³⁶⁴ and might theoretically cause some risk of transmitting serum hepatitis. These are technical difficulties however, which have already been largely obviated by appropriate technical advances. Finally, Malmros³⁶⁴ reports a relatively low tuberculin-conversion rate after cutaneous inoculation of BCG. Similar results obtained by Sigrid Holm are cited and criticized by Heimbeck,³⁶⁵ who calls attention to the low po-

tency of much of the tuberculin used in recent Scandinavian programs — a finding that is confirmed by Bøe.³⁶⁶ It is to be hoped that extensive parallel studies with the two routes for BCG inoculation will be carried out, so as to furnish a basis for their comparative evaluation, and that tuberculin of uniform potency will be available in all countries performing such studies, so that dependable comparisons can be made.

BCG cultures are not entirely stable, and difficulties with their maintenance have been reported.³⁶⁷ Furthermore, each batch of vaccine has a very short period of usefulness, usually set at eight to ten days. However, a Russian report³⁶⁸ offers some promise of providing a method for improving the stability of the filled product, and vacuum-dried preparations of high stability are now being prepared and tried in several laboratories.

Finally, it is of interest to watch developments in the experimental use of the vole acid-fast bacillus, a mycobacterium pathogenic only for murine animals. Several experimental studies³⁶⁹⁻³⁷¹ confirm the potency of the vole bacillus for animal immunization against tuberculosis, and one experimental study in man has been reported.³⁷² The subject has recently been reviewed by the investigator responsible for the original discovery.³⁷³

TYPHOID FEVER

Effectiveness of Vaccination

Holt⁷ has reviewed the major current trends in the control of typhoid fever by immunization, and brought up to date the classic chart of the incidence of typhoid and paratyphoid fevers in the United States Army since 1860. Except for a small outbreak in 1930, the annual rate in the Army has stayed consistently below 1 case per 10,000 strength since 1920, the peak rate in World War II being actually slightly below similar "peaks" in the pre-war years 1937 and 1940. Considering the insanitary conditions under which many troops were obliged to live in the field during combat, the absence of any significant rise in incidence of typhoid during this period is truly noteworthy. A "few hundred" cases occurred, all told, in the five years of World War II, however,⁷ some of which have been individually reported from a clinical standpoint³⁷⁴, others have also been studied in detail from epidemiologic and bacteriologic points of view.^{375, 376} The series reported by Tribby, Stock and Warner³⁷⁵ includes 45 United States Army personnel suffering from confirmed typhoid fever, and 10 with paratyphoid B fever. Such figures as these have led many observers to believe that typhoid immunization is of little value.

Cases among the immunized have likewise been reported from time to time in other groups. Margarik³⁷⁷ describes an epidemic in which 15.3 per cent of the vaccinated became ill, as against 28.5

that the diagnosis of the cause of death was not always reliable, and that the absence of morbidity data makes interpretation of the over-all results of the study unsatisfactory³⁴⁰ Furthermore, Wallgren³³¹ shows that the results, if corrected to exclude subjects who were exposed to tuberculous infection prior to vaccination, are as favorable as those of Rosenthal Tytler³⁴¹ prefers to draw no conclusions from Levine's study On the other hand, favorable reports such as that of Aronson and Palmer³³⁵ have also been subject to criticism Levine³⁴² and Wilson³⁴⁰ point out that in this study the cause of death was not always verified, the degree of exposure to tuberculosis in vaccinated subjects and controls was only "fairly well" balanced, and the intensity of exposure to contacts was not quantitatively evaluated The question is raised whether good results in American Indians "can legitimately be transferred to civilized peoples having a higher degree of genetic immunity and exposed, as a rule, to a lower risk of infection"³⁴⁰ However, this last comment comes from the same paper that concludes, from Levine and Sackett's data, that "under ordinary conditions in which the infants are brought up in a tuberculous environment (BCG) seems to confer little, if any, protection" — that is, an infant in New York City must be segregated from heavy exposure to tuberculosis until he has established immunity Either line of reasoning could be correct, but it is hard to accept both at once

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ferent method, would yield a product capable of protecting a mouse against 100 such challenge doses. These results are by no means unique, similar findings having been obtained elsewhere³³⁹. Thus, it is necessary to have definite knowledge of the potency of a vaccine, before its success or failure in a given situation can be properly assessed.

Advances continue to be made in the understanding of the antigenic components of the typhoid bacillus, and of the means by which they can best be utilized. Carlinfant³⁹⁰ has analyzed several rather technical aspects of the present knowledge of the much-explored but still inadequately understood "Vi" antigen, with particular reference to the selection of strains suitable for the production of vaccines of optimum antigenic composition. He offers evidence that vaccines killed by formalin or desiccation are superior in potency to those prepared by phenol and heat. Drysdale³⁹¹ has carried out a careful comparison of the standard phenol-killed vaccine and the alcohol vaccine developed by Felix.³⁹² No significant differences were found in mouse-protective potency between the two types of vaccine. Finally, Durand^{393, 394} has inactivated typhoid-paratyphoid A and B vaccine by the addition of di-ethyl or di-methyl-thiocarbamate, thereby apparently preserving the Vi antigen better than with heat killing or alcohol killing. These reports are but samples of the various studies on methods of improving the potency of typhoid vaccine, which are underway in many laboratories. It can be assumed with assurance that out of these studies there will come further improvements in the effectiveness of the vaccine.

Reactions

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Numerous studies cited above illustrate the antigenic effectiveness of this procedure. Its increased acceptance, coupled with the growing recognition of the importance of immunization in early infancy, has inevitably run headlong into the well established belief that diphtheria immunization in early infancy is relatively ineffective, owing to the persistence of maternally transmitted antibodies. This explanation has been strikingly confirmed by the studies of Cooke,⁹⁸ who administered combined diphtheria and tetanus toxoids to 284 infants from one to fourteen months of age. Tetanus antibodies developed equally well in all age groups, correlating with the complete absence of either passive or active tetanus immunity in the study group. The response to diphtheria toxoid was relatively poor in a significant percentage of the infants under six months old, however, and these subjects proved to be, for the most part, the very infants who were born with maternally inherited antibodies. Similar findings have been reported by di Sant' Agnese.¹⁸⁵

This evidence strengthens the case for separate administration of diphtheria toxoid after six months, pertussis vaccine preferably being given earlier (tetanus toxoid can be included at any convenient point). However, the findings of Bell⁷⁴ very clearly suggest that the adjuvant effect of combining a pertussis vaccine with diphtheria toxoid fully offsets — from a statistical standpoint — the opposing effect of passive immunity in early infancy. About 8 per cent Schick failures were observed by Bell in the very young infants receiving the

per cent of the unvaccinated, the cases in the former were said to have been mild, whereas in the unvaccinated they were generally severe. Jordan and Jones³⁷⁸ present a detailed description of 44 cases, among 80 observed during an outbreak in a contingent of vaccinated British troops, the course of the disease in this group was notable for its severity, but no information was available regarding the source, and hence the intensity, of the infection. Anderson et al.³⁷⁹ report 105 cases in inoculated British personnel in the Middle East, in whom the severity of the disease did not appear to have been altered by vaccination. Haedicke³⁸⁰ reports 4 rather mild and atypical cases among vaccinated laboratory workers. Typhoid infection in such personnel is not always mild, however, as was vividly brought home a few months ago by the death, from this disease, of a distinguished American specialist in enteric bacteriology, who had been repeatedly vaccinated. Rist³⁸¹ summarizes his observations in World War I, during which he saw 29 cases with 7 deaths among the vaccinated, and 27 cases with 5 deaths among the unvaccinated. No figures are given to indicate the relative numbers of vaccinated and unvaccinated persons from whom this sample is drawn, nor the conditions under which infection was contracted. Rendu,³⁸² whose iconoclastic analyses of immunization data of various kinds are noted in detail above under "Diphtheria,"^{66, 68} has compared the slow drop in typhoid incidence in Paris, where vaccination is said to have been used extensively, with the almost complete disappearance of the disease in New York City, where vaccination against typhoid is negligible but sanitary measures have been thoroughly applied. He cites numerous outbreaks of typhoid fever among vaccinated personnel, chiefly in the French Army but also in American troops^{374, 375} and states that "immunization of the American Expeditionary Forces has not prevented epidemics from occurring." He concludes that typhoid immunization is of little or no value. However, he is apparently unaware of recent reports in which the incidence of typhoid fever in vaccinated as against unvaccinated personnel could be compared.^{377, 383-385} all of which showed a significant lowering of the rate in immunized persons. Perhaps the most outstanding figures in this respect are those resurrected by Wilson and Miles³⁸⁶ from experiences during and before World War I. In British troops stationed abroad, up to 1913, 56 cases of typhoid fever had occurred among 10,378 vaccinated soldiers (0.54 per cent) as against 272 cases in 8936 uninoculated troops (3.05 per cent). In the French Army in 1915 the incidence was 0.095 per cent in the inoculated and 1.035 per cent in the uninoculated. More recently, Boyd³⁸⁷ has reported the experience of the British Middle Eastern Forces in 1940-42, in Allied and enemy prison camps. Several waves of typhoid fever occurred in Italian and German prisoners

held in British POW camps in this period. These outbreaks were later controlled in part by use of British vaccine, captured Italian vaccine having proved, on animal-protection tests, to be of inferior potency. On the other hand, some 25,000 British prisoners, in a highly insanitary camp near Benghazi, experienced no reported cases of typhoid fever, although they suffered about 12,000 cases of dysentery. The evidence strongly suggests that inoculation with a potent (British) vaccine gave a high level of protection, whereas the use of a less potent (Italian) vaccine, or no vaccine, led to high typhoid rates under insanitary conditions.

Preparation and Evaluation of Typhoid Vaccine

The somewhat conflicting results — and sharply conflicting opinions — cited above call for restatement of at least two elementary principles in the evaluation of any immunizing agent. The first is the fact that no such agent can ever be expected to give 100 per cent protection at all times. An agent of given efficacy may protect against an infecting dose of a given size or virulence for a variable but not limitless time, yet always there will be an infecting dose — or an interval since inoculation — that will overcome whatever protection was induced by the vaccination procedure employed. Hence the finding of cases of typhoid fever in vaccinated personnel means only that the vaccine does not always protect, this has been known for no less than thirty-five years. A satisfactory answer can only be obtained by comparison of genuinely comparable immunized and unimmunized groups — a situation that offers itself only rarely. The best controlled study of this type reported in recent years³⁸⁸ indicated that vaccination had given about 95 per cent protection against what was undoubtedly, to be sure, a rather small infecting dose. It is to be hoped that more controlled studies may be turned up as further opportunities arise.

The second factor in importance is apparent from the data cited by Boyd³⁸⁷ and from innumerable other studies — namely, that the potency of different batches of typhoid vaccine varies over a tremendous range. No world-wide agreement regarding the preferred method of potency testing has been reached, but the mouse-protection test — using either an actively immunized mouse, or a mouse inoculated with serum from an actively immunized person — is preferred in this country to the serum agglutinin titration. Bonnefoi et al.,³⁸⁹ at the Pasteur Institute, have recently confirmed the usefulness of the protection test. In the Division of Biologic Laboratories of the Massachusetts Department of Public Health it has repeatedly been demonstrated that a given batch of starting material could be made to yield a vaccine barely capable of protecting a mouse against the standard challenge dose of virulent typhoid organisms, whereas the same material, inactivated by a dif-

ferent method, would yield a product capable of protecting a mouse against 100 such challenge doses. These results are by no means unique, similar findings having been obtained elsewhere.³⁵⁹ Thus, it is necessary to have definite knowledge of the potency of a vaccine, before its success or failure in a given situation can be properly assessed.

Advances continue to be made in the understanding of the antigenic components of the typhoid bacillus, and of the means by which they can best be utilized. Carlinfant³⁹⁰ has analyzed several rather technical aspects of the present knowledge of the much-explored but still inadequately understood "Vi" antigen, with particular reference to the selection of strains suitable for the production of vaccines of optimum antigenic composition. He offers evidence that vaccines killed by formalin or desiccation are superior in potency to those prepared by phenol and heat. Drysdale³⁹¹ has carried out a careful comparison of the standard phenol-killed vaccine and the alcohol vaccine developed by Felix.³⁹² No significant differences were found in mouse-protective potency between the two types of vaccine. Finally, Durand^{393, 394} has inactivated typhoid-paratyphoid A and B vaccine by the addition of di-ethyl or di-methyl-thiocarbamate, thereby apparently preserving the Vi antigen better than with heat killing or alcohol killing. These reports are but samples of the various studies on methods of improving the potency of typhoid vaccine, which are underway in many laboratories. It can be assumed with assurance that out of these studies there will come further improvements in the effectiveness of the vaccine.

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Reactions to combined antigens continue to be the chief stumbling block to their general acceptance, although reports in this respect vary between both extremes. Volk⁴⁰¹ has reported on the use of nine different preparations comprising six different combinations of diphtheria and tetanus toxoids, scarlet-fever toxin, pertussis vaccine and typhoid vaccine, including a preparation containing all five antigens. He found — not unexpectedly — that the most severe reactions were related to inclusion of scarlet-fever toxin, that reactions to typhoid vaccine and diphtheria toxoid were commoner in adults than children, that children had fewer local and more general reactions than adults, and that five-antigen preparations could be administered safely to special groups. These are comparative rather than absolute results, and hence are somewhat difficult to translate into actual practice. However, the subjective nature of a "reaction" was clearly observed by Volk, who found that the incidence of absenteeism from school was markedly reduced by advance explanation of the probable effect of the inoculations.

Oral Immunization

The subject of immunization, which can become somewhat dry when expanded beyond a few para-

graphs, has been resuscitated by Dolman⁴⁰² in an extensive and stimulating review of oral immunization. The conclusion reached — that there is "no present justification for even occasional resort to oral immunization" — is approached philosophically as well as scientifically by Dolman, with whose opening remarks this review may draw to a close.

Mankind seems to enjoy placing a wide variety of objects into the mouth, but displays a widespread dislike of the needle puncture. From these impulses, which are perhaps primordial, may derive much of the preference likely to be shown for oral ingestion rather than hypodermic injection of specific therapeutic and prophylactic substances, whether narcotics, endocrines, sulfonamides, antibiotics, or immunizing agents.

One might add that mankind possesses a correlated primordial instinct, to try anything once, and usually more than once. Immunization procedures (by any route) are no exception to this rule. It is true that much may be accomplished by the use of unusual procedures under certain specified conditions — for example, the sucking of toxoid pastilles for booster immunization.^{78, 79} However, if there is any one major theme running through the varied components of this review, it is that much is yet unknown in the field of active immunization, that decision is indeed difficult, and that experiment can without doubt at times be perilous. Much disappointment and disillusion may be avoided, if the discerning physician will insist that the experimental evidence be adequate, before introducing a new procedure into his practice. One needs only to recall the history of "cold vaccines," liquid pertussis antigen, "undenatured bacterial antigen" or the two-dose schedule for fluid diphtheria toxoid — not to mention the currently receding wave of high enthusiasm for influenza vaccine — to realize once again how much energy both the doctor and the patient can expend on bright but unfulfilled hopes in this field.

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combined vaccine, as against 10 per cent failures in the older infants receiving the unmixed toxoid. There is now much additional evidence that combined antigens exert a potent effect in neonatal immunization, although the effect is in general less marked than that obtained in somewhat older infants. The various studies of di Sant' Agnese^{94, 187, 188} on neonatal immunization present ample evidence to this effect, adequate antibody levels against both pertussis and diphtheria were produced in most subjects in both age groups, but were definitely higher in the older group with respect to both diseases (the response to tetanus toxoid was excellent in both groups, no difference being disclosed by the method of assay). A booster dose six months after primary immunization produced equally high diphtheria antitoxin titers in both age groups, wiping out the pre-booster difference, but the booster response to pertussis vaccine was definitely better in the older group. Among older infants, there is more extensive evidence that combined antigens are effective, two recent reports by di Sant' Agnese³⁹⁹ and Fleming and his associates³⁹⁸ being among the most thorough studies in this field. Meanwhile, the Study Committee on Multiple Antigens of the American Public Health Association has been conducting extensive quantitative field evaluations of various antigen combinations, under its sponsorship have appeared a preliminary summary of recommendations⁴⁰⁰ and a report on reactions caused by various combinations⁴⁰¹, it is understood that the full report of this committee may shortly be available.

Reactions to combined antigens continue to be the chief stumbling block to their general acceptance, although reports in this respect vary between both extremes. Volk⁴⁰¹ has reported on the use of nine different preparations comprising six different combinations of diphtheria and tetanus toxoids, scarlet-fever toxin, pertussis vaccine and typhoid vaccine, including a preparation containing all five antigens. He found — not unexpectedly — that the most severe reactions were related to inclusion of scarlet-fever toxin, that reactions to typhoid vaccine and diphtheria toxoid were commoner in adults than children, that children had fewer local and more general reactions than adults, and that five-antigen preparations could be administered safely to special groups. These are comparative rather than absolute results, and hence are somewhat difficult to translate into actual practice. However, the subjective nature of a "reaction" was clearly observed by Volk who found that the incidence of absenteeism from school was markedly reduced by advance explanation of the probable effect of the inoculations.

Oral Immunization

The subject of immunization, which can become somewhat dry when expanded beyond a few para-

graphs, has been resuscitated by Dolman⁴⁰² in an extensive and stimulating review of oral immunization. The conclusion reached — that there is "no present justification for even occasional resort to oral immunization" — is approached philosophically as well as scientifically by Dolman, with whose opening remarks this review may draw to a close.

Mankind seems to enjoy placing a wide variety of objects into the mouth, but displays a widespread dislike of the needle puncture. From these impulses, which are perhaps primordial, may derive much of the preference likely to be shown for oral ingestion rather than hypodermic injection of specific therapeutic and prophylactic substances, whether narcotics, endocrines, sulfonamides, antibiotics, or immunizing agents.

One might add that mankind possesses a correlated primordial instinct, to try anything once, and usually more than once. Immunization procedures (by any route) are no exception to this rule. It is true that much may be accomplished by the use of unusual procedures under certain specified conditions — for example, the sucking of toxoid pastilles for booster immunization.^{78, 79} However, if there is any one major theme running through the varied components of this review, it is that much is yet unknown in the field of active immunization, that decision is indeed difficult, and that experiment can without doubt at times be perilous. Much disappointment and disillusion may be avoided, if the discerning physician will insist that the experimental evidence be adequate, before introducing a new procedure into his practice. One needs only to recall the history of "cold vaccines," liquid pertussis antigen, "undenatured bacterial antigen" or the two-dose schedule for fluid diphtheria toxoid — not to mention the currently receding wave of high enthusiasm for influenza vaccine — to realize once again how much energy both the doctor and the patient can expend on bright but unfulfilled hopes in this field.

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The Secretary moved that the report of the Committee on Membership as presented to the Executive Committee be approved by the Council. The motion was seconded, and it was so voted.

Joint Report of the Committees on Public Relations and Medical Economics — Dr Harold R. Kurth, Essex North, *Secretary*, and Dr Elmer S. Bagnall, Essex North, *Chairman*.

Dr Bagnall presented the report as printed in the circular of advance information to councilors and moved the approval of the fourteen points (Appendix No 3). The motion was seconded.

The President recognized Dr James C. McCann (Worcester), who spoke at length (Appendix No 4) and moved the adoption of the amendment. Dr Elmer Bagnall seconded the motion.

Dr Charles C. Lund (Suffolk) questioned the wording of the amendment. Dr McCann then changed the wording of the amendment as follows:

Section 4. Voluntary prepayment group health plans, embodying group practice and providing comprehensive service, when practicable, sometimes offer their members adequate medical care. No such plan shall be obstructed in procuring enabling legislation. No physician participating in such a plan shall be denied, by reason of participation per se, 1, membership in established medical societies, 2, hospital-staff appointments dependent upon such society membership, 3, consultation courtesies by nonparticipating physicians on the usual plane of ethical relationship.

The President called for a vote on the amendment as corrected by Dr McCann. The motion was carried.

The President recognized Dr Basil E. Barton (Norfolk), who offered the following resolution from the Norfolk District Medical Society and moved its adoption: "Resolved, that the Councilors of Norfolk District Society desire the clarification of points 8, 10 and 13 of the principles enunciated in the Joint Report of the Committee on Public Relations and the Committee on Medical Economics, before they can vote on it."

The motion was seconded, and it was so voted.

Dr Bagnall then clarified the principles from the point of view of the committees. Dr Barton questioned whether article No 13 referred to subsidies to schools or students — if the latter, Norfolk would object. Dr Bagnall said that could not be answered specifically.

Dr H. B. Harris (Norfolk) moved that principle No 13 be stricken from the record. The motion was seconded.

Dr Vlado A. Getting (Middlesex South) said that if the motion carried, Massachusetts stood to lose \$3,000,000 for public health.

Dr Leroy E. Parkins (Suffolk) moved that principle No 13 be referred back to the committee for a report at the next meeting of the Council. The motion was seconded and so voted by a show of hands 84 to 68.

Dr Carl Bearse (Norfolk) made a motion that principle No 10 be stricken out since it prohibited free choice of physician. The motion was seconded. The Secretary pointed out that these principles had been drawn very carefully, and after long discussion by a group well versed in the problems involved.

Dr Lund spoke in favor of the principle as now amended. The President called for a voice vote, and the motion was defeated.

Dr Albert A. Hornor (Suffolk) made a motion that the word "encourage" be substituted for the word "support" in principle No 8. The motion was seconded, and it was so voted.

Dr Bernard Appel (Essex South) made a motion to insert the words "voluntary prepayment" before the word "plan" in principle No 10. The motion was seconded, and it was so voted.

The President then called for a vote on approval of the report as amended. The report was approved by voice vote.

Committee on Tax-Supported Medical Care — Dr Albert A. Hornor, Suffolk, *Chairman*.

Dr Hornor made a motion to approve the report (Appendix No 5). The motion was seconded.

Dr Bagnall expressed the wish that the committee would further discuss regular office fees for multiple first visits in home or office, and thereafter full fee for one patient and \$1.00 for each additional patient. Dr Hornor promised such discussion. The President put the question, and the motion was carried.

Committee on Legislation — Dr Curtis C. Tripp, Bristol South, *Co-chairman*.

Dr Tripp submitted the report as printed (Appendix No 6) and moved its approval. The motion was seconded and so voted.

Subcommittee on National Legislation — Dr Elmer S. Bagnall, Essex North, *Chairman*.

Dr Bagnall moved the adoption of the report as printed (Appendix No 7). The motion was seconded and so voted.

Committee on Publications — Dr Richard M. Smith, Suffolk, *Chairman*.

Dr Smith moved approval of the report as printed (Appendix No 8). The motion was seconded, and it was so voted.

Committee on Arrangements — Dr Harold G. Giddings, Middlesex South, *Chairman*.

Dr Giddings moved for approval of the report as presented (Appendix No 9). The motion was seconded, and it was so voted.

MASSACHUSETTS MEDICAL SOCIETY

PROCEEDINGS OF THE COUNCIL

Annual Meeting, May 23, 1949

THE annual meeting of the Council was called to order by the President, Dr Daniel B Reardon, on Monday, May 23, 1949, at 7 00 p m, in the Ballroom of the Sheraton Hotel, Worcester

Two hundred and three councilors were present (Appendix No 1)

After opening the meeting, the President read the following obituary

JOHN HUGHES — Dr John Hughes, associate medical examiner and a practicing physician and surgeon in Pittsfield for twenty-five years, died suddenly on February 12 in Bristol, Rhode Island, where he was visiting his mother, who was seriously ill. He was sixty-six years old.

A native of Bristol, Rhode Island, Dr Hughes was born on January 21, 1883, son of Elizabeth Hamill Hughes and the late John J Hughes, and had lived in Pittsfield for more than a quarter of a century. He was a graduate of Providence High School, and had received his degree from University of Vermont College of Medicine in 1905. He took postgraduate work at the New York Postgraduate Hospital. He came to Pittsfield from Holyoke in 1924, where he had practiced for fifteen years. In 1937 he was appointed associate medical examiner by Governor Charles F Hurley.

He was a member of the Berkshire District Medical Society, and councilor from that district. He also belonged to the American Medical Association. Dr Hughes was a member of the staff of St Luke's Hospital and served as its president, and was also on the staff of the Pittsfield General Hospital.

At the request of the President, the Council stood in silent tribute to the departed member.

The President then announced the following interim appointments, which were approved by vote of the Council.

To the Committee to Meet with Massachusetts Nurses Association

Dr Richard B Cattell, *Chairman*
Dr Peirce H Leavitt
Dr David L Belding
Dr William F Wood
Dr Joseph A Holmes

Co-ordinating Committee

Dr Frank H Lahey, *Chairman*
Dr Charles J Kickham
Dr Leland S McKittrick
Dr Patrick J Sullivan
Dr John J Curley
Dr Walter G Phippen
Dr Frank W Snow
Dr Earle M Chapman
Dr Daniel B Reardon
Dr Arthur W Allen
Dr Donald Munro
Dr H Quimby Gallupe
Dr Eliot Hubbard, Jr
Dr Norman A Welch
Dr Elmer S Bagnall
Dr David L Belding
Dr Vlado A Gettung
Dr Augustus Thorndike
Dr Charles G Hayden

Dr Henry A Robinson
Dr Harold R Kurth
Dr Curtis C Tripp
Dr Joseph Garland
Dr John F Conlin

The Secretary presented the record of the meeting of the Council of February 2, 1949, as published in the *New England Journal of Medicine*, issue of April 7, 1949, and moved its acceptance. The motion was seconded, and it was so voted.

REPORTS OF COMMITTEES

Committee on Nominations — Dr Albert A Hornor, Suffolk, *Chairman*

The committee convened at 8 Fenway on April 13, 1949, and nominated the following officers of the Society for the year 1949-1950.

President, Dr Arthur W Allen
President-elect, Dr Leland S McKittrick
Vice-president, Dr Albert A Hornor
Secretary, Dr H Quimby Gallupe
Treasurer, Dr Eliot Hubbard, Jr
Assistant treasurer, Dr Norman A Welch
Orator, Dr John W O'Meara

Dr Hornor moved the acceptance of the report. The motion was seconded, and it was so voted. It was moved and seconded that the nominations be closed. It was so voted. It was moved that the Secretary cast one ballot for the list of nominees as presented. The motion was seconded, and it was so voted. The Secretary cast one ballot as directed.

Dr Reardon then presented Dr Arthur W Allen as the next president. Dr Allen replied that the vote of confidence was deeply appreciated and that no member of the Society receiving this great honor could possibly fail to be duly impressed. Dr Allen then gave an address, which was published in the June 16 issue of the *Journal*.

Dr Reardon then presented the other elected officers, and asked Dr Donald Munro to escort Dr Leland S McKittrick to the platform.

Executive Committee — Dr H Quimby Gallupe, Middlesex South, *Secretary*

The Secretary submitted the report of the committee (Appendix No 2), which met on April 20, 1949. He stated that 14 members of the committee were present at the meeting.

The Council by vote and without debate approved of the actions of the Executive Committee under its new business.

Dr Reardon put the question of the second amendment, and it was so voted. Dr Reardon put the question of the first amendment, and it was so voted.

Dr Ward then moved that Section 5 of the report be approved. The motion was seconded, and it was so voted.

Dr Ward then moved that the Council approve of the resolution concerning diabetes detection. The motion was seconded, and it was so voted.

Dr Ward then made a motion to approve the entire report as amended. The motion was seconded, and it was so voted unanimously.

Committee on Medical Defense — Dr Horatio Rogers, Suffolk, *Chairman*

Dr Rogers submitted the informational report as printed and moved its approval (Appendix No 15). The motion was seconded, and it was so voted.

Committee on Society Headquarters — Dr Frank R Ober, Suffolk, *Chairman*

Dr Ober presented the report (Appendix No 16) as printed. The Secretary then showed slides of the proposed location and buildings of the Boston Museum of Science on the banks of the Charles River at the dam. Dr Ober made a motion that the Council approve exploration of the possibilities implicated and report the findings at a future meeting of the Council. The motion was seconded, and it was so voted.

Committee on Industrial Health — Dr Daniel L Lynch, Norfolk, *Chairman*

Dr Lynch presented the report as printed (Appendix No 17) and moved its approval. The motion was seconded, and it was so voted. Dr Lynch made a motion that the Council approve the formation of a section on industrial health. The motion was seconded, and it was so voted.

Committee to Meet with the Massachusetts Hospital Association — Dr Albert E Parkhurst, Essex South, *Chairman*

Dr Parkhurst presented the informational report as printed (Appendix No 18) and moved its acceptance. The motion was seconded, and it was so voted.

Committee on Maternal Welfare — Dr Duncan Reid, Suffolk, *Chairman*

Dr Reid was not present. The President declared the report (Appendix No 19) informational. It was moved and seconded and voted to accept the report.

Committee on Post-Graduate Medical Education — Dr W Richard Ohler, Norfolk, *Chairman*

Dr Ohler presented his informational report as printed (Appendix No 20) and moved its acceptance. The motion was seconded, and it was so voted.

Committee on Medical Economics — Dr Elmer S Bagnall, Essex North, *Chairman*

Dr Bagnall presented the report as printed (Appendix No 21) and moved its acceptance. The motion was seconded, and it was so voted.

Committee to Make Recommendations as to Future Directors of the Blue Shield — Dr Leland S McKittrick, Suffolk, *Chairman*

Dr McKittrick presented his report as printed (Appendix No 22) and moved the appointments of the names submitted to become directors of Blue Shield, as indicated, until 1952 or 1951. The motion was seconded, and it was so voted.

Committee on School Health — Dr Ernest M Morris, Middlesex South, *Chairman*

Dr Morris presented the report as printed (Appendix No 23) and moved its acceptance. The motion was seconded, and it was so voted.

Subcommittee of the Executive Committee on Blue Cross-Blue Shield Problems — Dr Charles J E Kickham, Norfolk, *Chairman*

Dr Kickham presented his report as printed (Appendix No 24). He stated that for better public relations the whole aspect of fees should be investigated, as well as charges made to Blue Shield subscribers with incomes just over the fixed minimum.

He moved adoption of the recommendation as printed, "That a subcommittee of the Committee on Public Relations be constituted to investigate the problem and recommend an appropriate remedy." The motion was seconded.

Dr Arthur Allen said he approved and offered an amendment to the effect that the proposed committee explore the whole question of fees throughout the Commonwealth.

The motion was seconded, and it was so voted. The President then called for a vote on approval of the whole report as amended. It was so voted.

Committee on By-laws and Council Rules — Dr Edward P Bagg, Hampden, *Chairman*

Dr Bagg submitted the report (Appendix No 25) and added:

In addition to that, you received copies of the by-law changes that were approved at previous meetings of the Council. I should like to ask you to accept two corrections to the latter. In order to clarify the position of the new Committee on By-laws and Council Rules, I request that you allow the change from the word "under" to "to", there was omitted in the amendment, Chapter IV, Section 3, the word "on" in front of "by-laws". Therefore, it will read, "Resolved, that Chapter IV, Section 3 of the by-laws be, and hereby is, amended by the deletion of the word "and" (in line 9, page 14), after "Finance" and by the addition to the enumeration of standing committees the following words, "on by-laws and council rules."

The motion was seconded, and it was so voted. Dr Bagg then made the following motion:

Committee on Ethics and Discipline — Dr Ralph R Stratton, Middlesex East, *Chairman*

Dr Stratton moved adoption of all but the last paragraph of the report as printed (Appendix No 10) The motion was seconded, and it was so voted

Dr Stratton then moved to amend the report by striking out the last paragraph and substituting the following

About November 1, 1948, the committee received from the Eye and Ear Infirmary of the Massachusetts General Hospital a code of ethical conduct that was to govern them in their public relations They requested our examination of this code in relation to the code of ethics of the Massachusetts Medical Society

This code was studied and discussed at the meeting of the Committee on Ethics and Discipline on December 1, 1948 After this discussion, the committee unanimously voted that the code as proposed did not violate any of the provisions of the code of ethics of the Massachusetts Medical Society, nor of those of the principles of medical ethics of the American Medical Association

At the request of the Council, the matter was reconsidered at a meeting of the Committee on Ethics and Discipline on February 16 The Committee again reaffirmed that the code proposed by the Eye and Ear Infirmary did not violate the provisions of the code of ethics of the Massachusetts Medical Society, nor those of the principles of medical ethics of the American Medical Association

The motion was seconded.

Dr Donald Munro (Suffolk) stated that this amendment had cleared up objections to the report, but that there was a need for a code governing publicity that would be available to all hospitals, and he offered a second amendment as follows

That a committee of five be appointed by the President from representative districts of the Commonwealth to write a Massachusetts Medical Society Code to govern publicity They shall report at the next meeting of the Council

This motion was seconded, and it was so voted

The President then put the question of the first amendment, and it was so voted

Committee on Medical Education — Dr Chester S Keefer, Suffolk, *Chairman*

Dr James M Faulkner (Norfolk), for Dr Keefer, submitted the report as printed (Appendix No 11) and moved its adoption The motion was seconded, and it was so voted

Advisory Subcommittee on Medical Education — Dr Isaac R Jankelson, Norfolk, *Chairman*

Dr Jankelson submitted the majority and minority reports as printed (Appendix No 12) and moved their acceptance The motion was seconded, and it was so voted

Dr Jankelson then moved for the approval of the second recommendation in the majority report The motion was seconded, and it was so voted Dr Jankelson then moved the approval of the first recommendation of the majority report as the one

that had aroused the discussion and the disagreement by one committee member The motion was seconded, and it was so voted

Committee on Public Health — Dr Roy J Ward, Worcester, *Chairman*

Dr Ward presented the report as printed (Appendix No 13) Dr Ward then moved the approval of the first recommendation concerning the use of BCG vaccine by the Public Health Department of the City of Boston The motion was seconded, and it was so voted

Dr Ward moved approval of the second recommendation that greater emphasis be placed on education in the subject of nutrition in health The motion was seconded, and it was so voted

Dr Ward moved approval of the third recommendation concerning the pilot health clinics and further that a subcommittee of the Committee on Public Health representing the eighteenth districts to carry out the program be appointed and that the committee have power to act The motion was seconded

Dr Barton (Norfolk) moved the adoption of the following resolution "Resolved, that the councilors of the Norfolk District request from the Council an explanation of the mechanism of the origin and activation of pilot clinics proposed in the report of the Committee on Public Health before they can vote on it" The motion was seconded

Dr Ward then stated that it was the hope of his committee that a pilot clinic could do at one process what now is done in many for the detection of diabetes, heart disease, tuberculosis and so forth

Dr Appel said he thought the appointed committee should not be given power to act Dr W A R Chapin agreed with him

Dr Earle M Chapman (Suffolk) spoke at length for the recommendation Dr John J Curley (Worcester North) said the Executive Committee favored the pilot clinic plan Dr Lawrence Dame (Franklin) agreed with Dr Curley

The Secretary then read a document entitled "Health-Protection Clinics" (Appendix No 14), which had been presented to the Executive Committee Dr Maurice Fremont-Smith (Suffolk) spoke in favor of the plan Dr Donald Munro said he favored the plan as long overdue

Dr Leroy E Parkins moved an amendment that "pilot clinic" be substituted for "pilot clinics" The motion was seconded Dr Parkins moved a second amendment that a committee appointed be empowered to act in accordance with the eight principles in Dr Getting's program This motion was seconded

Dr Arthur Allen said he believed there should be more than one clinic Dr Parkins agreed to change his amendment to read "not more than five pilot clinics"

J C Merriam
Dwight O'Hara
Fabian Packard
L S Pilcher
Max Ritvo
G A Saunders
J H Townsend
C F Walcott
R H Wells

H A Robinson
R G Vinal

PLYMOUTH

Samuel Gale
P H Leavitt
C D McCann
G A Moore

SUFFOLK

H L Albright
M D Altschule
A W Allen
T J Anglem
C H Bradford
W E Browne
A M Butler
A J A Campbell
E M Chapman
M H Clifford
Joseph Garland
A A Hornor
H A Kellv
H E Kennard
T H Lanman
R I Lee
C C Lund
L S McKittrick
Donald Munro
F R Ober
L E Parkins
L E Phansenf
H S Pittman
J H Pratt
J J Regan
Horatio Rogers
H F Root
C G Shedd
R M Smith
Conrad Wesselhoeft

WORCESTER

A W Atwood
F P Bousquet
Jacob Brem
J B Butts
F B Carr
E J Crane
Paul Dufault
G R Dunlop
W J Elliott
John Fallon
Donald Hight
Thomas Hunter
H L Kirkendall
D G Ljungberg
J A Lundv
J C McCann
D K McCluskey
J M Olson
F A O'Toole
G L Richmond
N S Scarcello
J J Tegelberg
R J Ward
B C Wheeler

NORFOLK

A. A. Abrams
B E Barton
Carl Bearse
Elizabeth Broyles
G L Doherty
Albert Ehrenfried
J M Faulkner
P S Foisie
D L Halbersleben
J A Halsted
H B Harris
C G Havden
Susannah Friedman
R J Heffernan
P J Jakmauh
I R Jankelson
C J Kickham
C J E Kickham
D L Lionberger
D S Luce
C M Lydon
T F P Lyons
D L Lynch
H L McCarthy
F J Moran
H R Morrison
D J Mullane
H A Novack
W R Ohler
E E O'Neil
R S Palmer
H A Rice
L A Sieracki
S L Skvirsky
E C Smith
Kathleen Snow
J W Spellman
A R Stagg
W J Walton
N A Welch
W A White, Jr
G F Wilkins
P R Withington
E T Wisman

NORFOLK SOUTH

F A Bartlett
D L Belding
Harry Braverman
R L Cook
Frederick Hinchliffe
E K Jenkins
N R Pillsbury
D B Reardon

The Secretary read a letter from Dr Lawrence R Dame requesting a new section on ophthalmology and otolaryngology. On a motion duly made and seconded, it was voted to establish such a section.

The Secretary then stated that at a meeting of district society secretaries it was voted to request the Executive Committee to consider recommending annual registration of physicians in Massachusetts. The Secretary pointed out that once the Council had voted in favor and once had voted against annual registration. He said the General Court might write a bill for annual registration that might not be satisfactory to the Society.

The Secretary stated that no list of registered physicians is available for any purpose. Dr John Fallon, Worcester, said he was registered every year in Minnesota, that it was no burden to him, that it helped to keep out the unregistered illegal practitioners and that he favored it. The President stated that nurses and dentists register annually.

The Secretary pointed out that the legislation could include the publication of the list of registered physicians, and that such a list would be helpful to the Society. Dr John Curlev, Worcester North, moved that the Committee on Legislation and our legal counsel write a bill calling for annual registration. The motion was seconded.

Dr Dame, Franklin asked what would happen to a doctor who was late in registering. The Secretary stated that punishment, if any, would have to be written in the bill. Dr Dame pointed out that now physicians must be licensed in cities and towns and that not to be so licensed causes trouble for the doctor. Dr Welch said he had helped to defeat a similar bill and that the Board of Registration could not use the money obtained from fees for investigations. Dr Welch said that the defeated bill was poorly drawn. Dr Munro agreed with Dr Welch that the bill was bad and might have meant that a doctor would have to be re-examined if he failed to re-register.

Dr Gallupe stated that a doctor is registered only once and that re-registration is not accompanied by re-examination. He pointed out that no board has the full use of monies taken in, and that the board cannot investigate unregistered practitioners since that is the duty of the state police. Dr Charles J E Kickham said we shouldn't approve a bill until one is written. Dr Welch said bills are often changed markedly by the legislature. Dr Reardon stated the motion we approve of annual registration and recommend that a bill be written by the Committee on Legislation. The motion was seconded and defeated 11 to 3.

Dr Reardon then stated that the fourth matter for consideration under new business was referred to the committee by a meeting of officers and delegates of the Society to which the editor of the *Journal*, Blue Shield and Massachusetts National Physicians Committee members and critics of the American Medical Association leadership had been invited. It was the opinion of this group that the Executive Committee should consider recommending that our delegates to the American Medical Association be instructed to urge the House of Delegates to separate Dr Fishbein from any official position in the American Medical Association organization, take proper steps to end the National Physicians Committee hasten the plan for national enrollment of Blue Cross-Blue Shield as outlined by Dr Paul Hawley, reorganize the Council on Medical Service of the American Medical Association.

Dr Reardon stated that the second recommendation had been accomplished by the National Physicians Committee itself. Dr Munro asked if the item might be considered separately. Dr Reardon gave consent.

The Secretary stated that criticism concerning Dr Fishbein had been voiced at the joint meeting held on February 9 of the committees on Public Relations and Medical Economics, but that at a meeting of our co-ordinating committee the opinion was expressed that it would be better now to fight for things rather than to fight *against* other doctors. It is better public relations to let the public know we are not fighting amongst ourselves.

Dr Munro made a motion to disapprove of the first recommendation. The motion was seconded. Dr Munro thought it would be a tactical error to carry out the recommendation at this time. The President put the question to vote, and the motion was carried.

Dr Reardon then presented the third recommendation. Dr John Curlev said he believed Dr Elmer Hess would

APPENDIX NO 2

REPORT OF THE EXECUTIVE COMMITTEE

President Reardon called the meeting to order, and the Secretary called the roll. Councilors from Barnstable, Berkshire, Hampshire and Plymouth were absent. The Secretary stated that no business had been referred from the Council.

Under new business, the Secretary read a letter from Dr Walter E. Barton president of the Massachusetts Psychiatric Society, requesting the establishment of a section on psychiatry and neurology. It was moved and seconded that such a section be established. It was so voted without discussion.

In order to avoid as many errors as possible, I move that the proposed by-laws shall be submitted, for correction of any errors in form, to an assistant editor of the *New England Journal of Medicine*. I also move authorization and the publication of a new volume containing the Digest, By-laws, Code of Ethics and Medical Defense Act of the Society, and the Principles of Medical Ethics of the American Medical Association

The motion was seconded and so voted

Dr Bagg moved for approval of the report as a whole. The motion was seconded, and it was so voted

Committee on Diabetes—Dr Howard F Root, Suffolk, *Chairman*

Dr Root presented the report as printed (Appendix No 26) and moved its acceptance. The motion was seconded, and it was so voted

Committee on Veterans Affairs—Dr Harvey A Kelly, Suffolk, *Chairman*

Dr Kelly presented the report as printed (Appendix No 27) and moved its acceptance. The motion was seconded, and it was so voted

REPORT OF THE TREASURER

Dr Eliot Hubbard, Jr, Middlesex South, presented the report as printed (Appendix No 28) and moved its acceptance. The motion was seconded, and it was so voted

AUDITOR'S REPORT

Dr Gallupe read the report of the Auditing Committee (Appendix No 29), Dr Howard B Jackson, Norfolk, *Chairman*, and moved its acceptance. The motion was seconded, and it was so voted

The Secretary then moved that the report of the Executive Committee as amended be approved. The motion was seconded, and it was so voted

NEW BUSINESS

The President recognized Dr Barton, of Norfolk, who offered the following resolution presented by the Councilors of the Norfolk District Medical Society: "Resolved, that Norfolk District requests the Council for a delineation of the developments that have taken place regarding the report of the Committee on Special Services," and moved its acceptance. Dr Reardon said that under the Council Rules he would refer the resolution to the Committee to Meet with the Massachusetts Hospital Association

The President then recognized Dr William Elliot, Worcester, who presented the following resolution

That the committee from the Massachusetts Medical Society to confer with the Massachusetts Hospital Association be instructed to take steps to expedite the acceptance and practice of the principles enunciated by the Committee to Study Special Services, that the Secretary send a copy of the report of the Committee to Study Special Services to the Massachusetts Hospital Association

with the specific request that action be taken on the report by that body, and that the committee from the Massachusetts Medical Society to confer with the Massachusetts Hospital Association be requested to report to the Council at the October, 1949, meeting

Dr Reardon referred the resolution to the Committee to Meet with the Massachusetts Hospital Association

Dr Reardon then presented Dr Arthur W Allen, the president-elect, who read his committee appointments and the chairmen and secretaries of the new sections, and the delegates to the American Medical Association (Dr Allen's appointments were acted upon, and all approved at the annual meeting of the Society the next day)

The President said that if there were no further matters of new business, a motion to adjourn was in order. The motion was made, seconded and so voted at 11 00 p m

H QUIMBY GALLUPE, *Secretary*

APPENDIX NO 1

BERASHIRE

D N Beers
P J Sullivan

BRISTOL NORTH

M E Johnson
W M Stobbs

BRISTOL SOUTH

J C Corrigan
A J Pothier
C C Tripp

ESSEX NORTH

E S Bagnall
R E Blais
J A Bradley
A P George
H R Kurth
R C Norris
L C Peirce
F W Snow
L T Stokes
F N Sweetsir
C A Weiss

ESSEX SOUTH

Bernard Appel
S N Gardner
R P Hallett
A E Parkhurst
E D Reynolds
H D Stebbins
C J Twomey

FRANKLIN

J E Moran

HAMPDEN

F H Allen
E P Bagg
R L Barrett
W A R Chapin
J L Chereskin
G B Corcoran
A J Douglas
E C Dubois
A F G Edgelow
Frederic Hagler
A G Rice

G L Schadt
H N Simpson
G L Steele

HAMPSHIRE

J R Hobbs
E J Manwell
L B Pond

MIDDLESEX EAST

J L Anderson
T P Dexlin
Robert Dutton
E M Halligan
K L MacLachlan
H L Mueller
M J Quinn
R R Stratton

MIDDLESEX NORTH

W M Collins
S A Dibbins
L J Hall
L F King
A J Stewart
J D Sweeney

MIDDLESEX SOUTH

E W Barron
J M Baty
J D Bennett
W O Blanchard
G F H Bowers
Madeline R Brown
R N Brown
R W Buck
E J Butler
E A Cooney
C L Derick
A G Engelbach
C W Finnerty
J M Flynn
H Q Gallupe
V A Getting
H G Giddings
H W Godfrey
J L Golden
Eliot Hubbard, Jr.
F R Jouett
H A Kontoff
A A Levi
A N Makechnie
J H McSweeney

Dr Ward said the clinic would be carrying out the policies of the American Medical Association. Dr Getting said all that was asked for was approval in principle and not for the approval of a specific plan. Dr Lynch said the plan tied in with the report of the Committee on Diabetes and the Committee on Industrial Health, and he was strongly in favor of it. Dr Reardon put the question to a vote, and the motion was carried.

Dr Curley moved the endorsement in principle of the recommendation concerning local health unions and centers. The motion was seconded, and it was so voted. The Secretary then moved approval of the resolution beginning on line 31, through line 43, on page 13. The motion was seconded, and it was so voted.

The President then presented the report of the Committee on Medical Defense as informational, and it was accepted.

The President then presented the report of the Committee on Industrial Health with its resolution. The Secretary moved the acceptance of the report and approval of the resolution beginning on line 25, page 17. The motion was seconded, and it was so voted.

Dr Munro moved the approval of the resolution beginning on line 31, page 17. The motion was seconded, and it was so voted.

The President presented the report of the Committee to Meet with the Massachusetts Hospital Association as informational, and it was accepted.

The President presented the report of the Committee on Maternal Welfare, which was accepted as informational.

The President presented the report of the Committee on Postgraduate Education, and it was accepted as informational.

The President presented the report of the Committee on Medical Economics as informational, and it was accepted.

The President presented the report of the Committee to Make Recommendations as to Future Directors of Blue Shield. The Secretary moved that the nominations submitted be approved. The motion was seconded, and it was so voted.

The President presented the report of the Committee on School Health, and it was accepted as informational.

The President introduced Dr C J E Kickham, who presented the report of the Committee on Blue Cross-Blue Shield problems. Dr Kickham moved that the Executive Committee approve the recommendation beginning on line 19, page 23. This motion was seconded.

There ensued a long discussion concerning whether or not this matter was one of public relations or one for the Blue Shield local committees or the Committee on Blue Cross-Blue Shield problems. It was brought out in the discussion that complaints about excessive fees were not too many, but they were widespread and applied not only to Blue Shield cases but also to others, and that it was the opinion of most of the committee that the allegations should be investigated and a remedy suggested as a public-relations project. The President put the motion to a vote, and it was carried.

Dr Kickham then made a motion that the second recommendation, beginning on line 38, page 23, be approved in principle. The motion was seconded, and it was so voted without discussion.

Dr Reardon then presented the report of the Committee on By-laws and Council Rules. The Secretary moved the approval of the report. The motion was seconded, and it was so voted without discussion.

The President presented the report of the Committee on Diabetes. It was moved and seconded to approve the report with its resolution. It was so voted without discussion.

The President introduced Dr Harvey Kelly, who presented the report of the Committee on Veterans Affairs. He stated that it was the intention of his committee to have the material printed in the *Journal* for information to doctors. Dr John Curley and Dr Donald Munro objected because they believed this might be interpreted as interference by the Society in the practice of medicine by our doctors. Dr Munro moved that the report beginning on line 31, page 25, through line 47 be disapproved. The motion was seconded, and it was so voted.

Dr Munro moved that the first word "lastly" be deleted. The motion was seconded, and it was so voted without discussion.

Dr Munro then moved that the next recommendation of the report be approved after changing the fifth word in line 1 from "these" to "this". The motion was seconded, and it was so voted.

Dr Munro then moved that the last recommendation beginning on line 3, page 26, be disapproved. The motion was seconded, and it was so voted.

The President then introduced Dr Hubbard, who presented his report and moved its acceptance as informational. The motion was seconded, and it was so voted.

A motion to adjourn was made and seconded, and it was so voted at 5:15 p.m.

H. QUIMBY GALLUPE, *Secretary*

APPENDIX NO 3

JOINT REPORT OF THE COMMITTEE ON PUBLIC RELATIONS AND THE COMMITTEE ON MEDICAL ECONOMICS

The following principles were adopted on February 9, 1949 by the committees on Medical Economics and Public Relations of the Massachusetts Medical Society and a group of the staff of the Massachusetts General Hospital for presentation at the meeting of the Planning Committee of the American Medical Association on February 12, 1949.

1 We believe that the health of the people served by pre-payment insurance plans will be most benefited by medical care free of government administration and control.

2 We should like to call attention to the profligate waste and duplication in health programs operated by the Government in regard to both hospital beds and personnel as reported by the Hoover Commission. We believe that compulsory health insurance operated by the Government would result in similar inefficiency.

3 We believe that the manner of expression of policy on the part of the American Medical Association has served to diminish public confidence in that body to the serious concern of many of the members of the association.

We believe that the policy of the American Medical Association should be one of more active and enthusiastic support of constructive proposals for more equitable distribution of medical care.

Therefore, we suggest as constructive proposals worthy of support the following:

1 The objective of adequate medical care in our free society is to make available to everyone—regardless of race, color, creed, financial status or place of residence, every known essential preventive, diagnostic and curative medical service of high quality. The attainment of such medical care must necessarily be an evolutionary process which will require the co-operation of all concerned over a period of years.

2 The principle of voluntary prepayment health insurance should be the basic method of financing medical care for the large majority of the American people, in order to remove the burden of unpredictable sickness costs and abolish the economic barrier to adequate medical services.

3 The success of any plan for medical care is dependent on the mutual co-operation of the public, those rendering professional services and the administrative agencies. This co-operation can be obtained only if those rendering the services are convinced that they will have a continuing authoritative voice in the formulation and execution of policies and plans, thereby assuming their proper share of responsibility.

4 Voluntary prepayment group health plans, embodying group practice and providing comprehensive service, when practicable, offer to their members excellent medical care. Hence such plans should be encouraged.

5 The people have the right to establish voluntary prepayment plans on any basis guarded by legal restrictions necessary to assure proper standards and qualifications.

6 Provision of adequate medical care for those unable to obtain it by voluntary prepayment plans or by direct payment is the responsibility of the local or state government. Part of the burden of this responsibility may be assumed by charitable agencies. Federal grant-in-aid

present a favorable report on National Blue Shield at the American Medical Association Delegates meeting Dr Reardon said National Blue Cross is already a fact Dr Kickham stated that the committee on Blue Cross-Blue Shield Problems had made recommendations to the Society in favor of a national Blue Shield enrollment service Dr Fallon said he believed it would be wise to favor a national Blue Shield scheme and moved that in place of this recommendation, the executive committee approve in principle the idea of a national Blue Shield enrollment agency The motion was seconded, and it was so voted

Concerning the fourth recommendation Drs Fallon and Curley suggested that our delegates might do well to sit in at meetings of the Council and talk with its members Dr Fallon thought it better not to interfere at this time Dr Munro moved to lay this recommendation on the table The motion was seconded, and it was so voted

The Secretary said he had a letter requesting the Society to take action concerning the parking of doctors' cars without interference by the police The only solution offered by the Secretary was to have the letters "MD" precede the license number on the doctors' cars Dr Curley moved that this matter be laid on the table The motion was seconded and so voted

The Secretary then presented a request from the chairman of the Committee on Physical Medicine that his committee be discharged and replaced by a single committee on physical medicine and rehabilitation The Secretary suggested that this matter be left to the discretion of Dr Arthur Allen, whose duty it is to appoint committees for the ensuing year Dr Curley moved the matter be laid on the table The motion was seconded and it was so voted

The Secretary then stated that Dr Reardon wished the committee to approve of his appointment of a co-ordinating committee to carry out the educational campaign of the American Medical Association as follows Dr Frank Lahey, chairman, Drs Charles J Kickham, Leland S McKittrick, Patrick J Sullivan, John J Curley, Walter G Phippen, Frank W Snow, Earle M Chapman, Daniel B Reardon, Arthur W Allen, Donald Munro, H Quimby Gallupe, Elmer Hubbard, Jr, Norman A Welch, John F Conlin, Elmer S Bagnall, David L Belding, Vlado A Getting, Augustus Thorndike, Charles G Hayden, Henry A Robinson, Harold R Kurth, Curtis C Tripp, Joseph Garland

Dr MacLachlan moved the approval of this committee The motion was seconded, and it was so voted The Secretary said this committee wanted the Council to approve the educational campaign of the American Medical Association Dr Curley made the motion to approve, which was seconded, and it was so voted

The Secretary presented the report of the Committee on Membership and moved its acceptance The motion was seconded, and it was so voted

Dr Reardon then presented the joint report of the Committee on Public Relations and the Committee on Medical Economics Dr MacLachlan said Middlesex East District approved all except principle 13 Dr Fallon said he believed principle 13 had been approved by the American Medical Association essentially as it stands Dr Reardon said he believed the fourteen points answered our critics who say we have done nothing constructive Dr Fallon said he believed all these points could be found in the records of the Council on Medical Service Dr Munro moved approval of the report as printed The motion was seconded, and it was so voted

Dr Reardon then asked the committee to consider the report of the Committee on Society Headquarters, which asks for authority to explore the possibility of obtaining headquarters for the Society, the Library and the Journal and to report its findings at a future meeting of the Council The President stated that the committee had met with officers of the Boston Museum of Science to discuss the possibility of joining with them at their proposed site on the Charles River at the dam The President then introduced Mr Bradford Washburn, the director of the museum, who described the project and showed slides of the location and the proposed buildings He pointed out the advantages of the location, the available parking space and easy transportation facilities Dr Kickham moved that the committee be given authority asked for and to report back to the Council The motion was seconded, and it was so voted

The President presented the report of the Committee on Tax-Supported Medical Care Dr Hornor said the original fees had been increased and moved the approval of his committee recommendation The motion was seconded, and it was so voted

The President presented the report of the Committee on Legislation, and it was accepted as informational

The President presented the report of the Committee on National Legislation, which was accepted as informational

The President presented the report of the Committee on Publications and it was accepted as informational (The publication of the *Directory* had already been approved in the budget for 1949)

The President presented the report of the *New England Journal of Medicine*, which was accepted as informational

The President submitted the report of the Committee on Arrangements It was accepted as informational

The President presented the report of the Committee on Ethics and Discipline and pointed out that the committee had reaffirmed its approval of the code of the Eye and Ear Infirmary Dr Curley moved acceptance of the report Dr Dame asked if the Council would be asked to approve every such code, and the Secretary thought this code was set up as a standard, which would be acceptable to the Society Dr Curley's motion was seconded Drs Dame, Munro and Welch expressed disapproval of the code on the grounds that it would allow an institution to circumvent the code of ethics of the Society Dr Munro moved that the motion be amended to the effect that the report be accepted, but that lines 5 to 14 of page 8 be disapproved This motion was seconded, and it was so voted

The President presented the report of the Committee on Medical Education, which was accepted, and its nominations for recipients of the awards were approved

The President introduced Dr Jankelson, who presented the report of the Advisory Subcommittee on Medical Education and stated that the area of agreement on the committee was large and the area of disagreement was narrow (Dr Gardner was not present to present his views) All except Dr Gardner believed that the proper certification body was the Board of Neurology and Psychiatry, and all were agreed that licensure by the Commonwealth to practice clinical psychology should not be supported at this time The Secretary moved approval of the majority report of the committee The motion was seconded, and it was so voted It was then moved and seconded that the lines 11 to 22, page 12, of the minority report be disapproved It was so voted

The President introduced Dr Roy Ward, who presented the report of the Committee on Public Health Dr MacLachlan moved that the committee's endorsement in principle of the limited investigation of the use of BCG vaccine be approved The motion was seconded, and it was so voted

Dr Munro then moved to approve in principle the recommendation that more emphasis be placed on education in the subject of nutrition on the undergraduate and graduate levels This motion was seconded, and it was so voted

Dr Munro moved to approve the committee recommendation concerning pilot clinics beginning on line 14, page 13 The motion was seconded

Dr Getting then pointed out that the project would be a joint effort of the Society, the hospital association, the community hospital, the Cancer Society, the Heart Association and others, including the Department of Public Health The clinics could evaluate the health screen, which is now restricted to separate groups The clinic would help combat socialized medicine. It would co-ordinate the efforts of voluntary groups The clinic would do no diagnostic work, but the report would go to the family doctor for diagnosis and treatment X-ray study would probably be limited to chest films The clinic would be in a community hospital, and the doctors would be paid The clinic would be publicized as a joint effort in the local newspapers The size of the city would be determined by the groups or committee conducting the study The project is the result of study including Dr Magnuson's report on a national level There would be no charge at the clinic, but opportunity would be given for contributions Dr Getting said patients would be referred to the clinic by physicians Dr Merriam said that the heart clinic in Framingham was going well, was doing a lot of good and was without objection from doctors

economics prepayment for medical care, group practice, and comprehensive service.

Gentlemen, if you will read proposal 4, lines 5, 6, 7 and 8, in them you will see that the co-operatives seek as late as 1949, when there are increasing signs of impending victory for our philosophy and methods, to strike you in an unguarded moment from your present vantage point. Truly our columnist Bill Cunningham painted a true picture, if we accept this proposal, when he wrote "We seem to have an exquisite genius for getting things fouled up past any explaining, understanding, or unraveling, and, generally, at the most inopportune times."

To clarify our position both philosophically and strategically, I offer the following amendment to be substituted for lines 7 and 8 of Proposal 4. It is based on ten years of experience across the country. It lets the co-operatives go their way while we go ours. But it certainly does not give them approval or a euphonious "encouragement." It states the position of the Society taken under Dr. Phippen, president, when White Cross Co-operative started in Massachusetts, the position followed in succession by Dr. Lanman and myself as chairman of the Massachusetts prepayment enterprise on advice of doctors from Washington, D. C., who were embroiled in the Supreme Court fiasco.

I move that, leaving intact lines 5 and 6 of Proposal 4, page 2, we amend lines 7 and 8 to read as follows:

sometimes offer their members adequate medical care. No such plan shall be obstructed in procuring enabling legislation. No physician participating in such a plan shall be denied, by reason of participation per se, (1) membership in established medical societies, (2) hospital-staff appointments dependent upon such society memberships, (3) consultation courtesies by nonparticipating physicians on the usual plane of ethical relationships.

If the common-sense policy enumerated herein had been followed by American medicine for the past ten years, we should not have landed in the courts. We should not be subject to tactics seeking to extract from us approval of consumer co-operatives, we should have been spared 80 per cent of our difficulties, and we should be today in a much better strategic position before the people of our country.

APPENDIX NO 5

COMMITTEE ON TAX-SUPPORTED MEDICAL CARE

As a result of conferences with Mr. Charles Dunn, attorney of the Massachusetts Medical Society, and study of the law covering veterans' services it was learned that the fees for veterans' services are fixed by the Commissioner and may be paid only in accordance with the Commissioner's regulations concerning prior authorization, emergency and so forth. The one exception to this is explained in the following quotation from a letter from Commissioner O'Day:

The city or town is granted the privilege of paying aid in addition to what the Commissioner may authorize. When this is done that increase must be borne entirely by the place of settlement. If there are extenuating circumstances in a case, and the city or town wishes to pay more than we have originally authorized, and they clarify the situation, I usually meet that situation by increasing our allowance, but this would not apply to medical expense. Medical expense is always considered separate from the budget that is allowed for support and care.

This part of the law gives the Commissioner the right to determine any amount which he considers proper and lawful. The question before you, I presume, is whether a city or town would not have the right to pay in addition to the schedule that I have set up, and to that I would say that they have that right, but any amount that they pay over and above our schedule would not be shared by the Commonwealth. I presume that there are some towns that will probably pay higher than my schedule, but if they do, the amount they pay in excess of my rate will have to be their responsibility.

After considering the above, two members of the Committee on Tax-Supported Medical Care conferred with Com-

missioner O'Day with the result that he is willing to change the directive to permit the following changes:

Note these changes, kindly refer to Page 2 of my Medical Directive. *Fee Schedule*

Home Visit change to \$4

Office Visit change to \$3

Below entitled *Night Calls* \$1 additional to \$2 additional and change time limitations from between 9 p.m. and 7 a.m.

The Committee on Tax-Supported Medical Care recommends to the Council that it approve the fees for veterans' services as recommended by the Commissioner of Veterans' Services for the present.

FREDERICK S. HOPKINS
FRANCIS P. MCCARTHY
FRANK W. SNOW
ALBERT A. HONOR, *Chairman*

APPENDIX NO 6

COMMITTEE ON LEGISLATION

The Legislative Committee has held several meetings during the year and has considered many bills of importance to medical practice. Our most important effort was directed toward the defeat of the chiropractor bill, which would have established a board of registration for chiropractors in the Commonwealth. This bill was heard before the public-health committees, and aside from our regular speakers several district presidents responded to our request and spoke in opposition.

Definite action was also taken on the vaccination, viro-section and open-hospital bills and on a bill to exempt the Blue Shield from taxation, and opposition was made to several bills proposing further legislation to allow future graduates of substandard medical schools to take examinations before the Board of Registration. Bills before the national Congress such as S5 are in the hands of the subcommittee on national legislation.

The committee believes that the physicians of the Commonwealth should present a united front in making recommendations to committees of the Legislature. This committee makes a careful study of all bills having important medical significance and arranges to make appearances before committees of the Legislature when they hear such bills. While it is the privilege of any individual to express himself at these hearings, it is confusing to the committees of the Legislature to have groups of physicians appearing on both sides of the same question. This committee will be glad to discuss proposed legislation with those who are to make appearances in order that they may understand the reasons for the position that this committee takes.

It has been suggested that a poll of the action of the legislators on important medical bills be published in the *New England Journal of Medicine*. It has been the opinion of this committee that such publicity is unwise because of its danger of antagonizing individual legislators to future bills in which we may have an interest. Such information is usually in the hands of the committee and may be obtained through the district legislative councilors.

The personal contact between physicians and their representatives in the General Court is the most important influence in guiding legislation and is of more importance than the formal appearance that we make at the State House. We urge that each district society arrange to have local physicians interest themselves in the work of their senators and representatives so that they may build up a friendly basis for the future discussion of important bills relating to the public health and the practice of medicine.

ALFRED L. DUNCOMBE
CURTIS C. TRIPP, *Co-chairman*

APPENDIX NO 7

SUBCOMMITTEE ON NATIONAL LEGISLATION

At a meeting on February 17, 1949 the available bills on health legislation were screened. It was voted to favor in principle:

(1) S 522 and similar bills for Local Health Units, provided the services were delineated, (2) HR 325 and

to state programs administered by state boards of health is an acceptable method of helping to meet this responsibility.

7 The medical care of those who are able to purchase it by voluntary prepayment plans or by direct payment is the responsibility of the individual.

8 The federal Government, should, whenever possible, support voluntary prepayment programs for hospital and medical care.

9 Eligibility for receiving benefits under a program aided by federal grants should be determined by the individual states or communities.

10 The patient shall have free choice of his physician, group of physicians, clinic or hospital from among those participating in any plan, provided that the physician, group of physicians, clinic or hospital shall have the right to refuse or accept the patient.

11 Physicians and other qualified persons rendering medical care shall receive adequate remuneration for their services.

12 The physician shall be free to elect or reject without prejudice participation in a medical care plan. The rights of the physician as to the choice of methods by which he is to be paid shall be fully protected.

13 We agree that the federal Government now should subsidize medical and nursing education, medical indigents, health and diagnostic centers, including mental, where not now adequate.

We believe effective organizations of state and district health councils would immeasurably improve the community concept of local health needs. The initiative of the people themselves, and especially of the medical and public-health personnel, must provide the spark.

14 The Massachusetts Medical Society looks upon these basic principles as essential to the development of any successful medical-care plan and, as guides by which to evaluate medical-care plans that may be proposed in the future, with the understanding that changing conditions may require their later revision.

We further urge that our delegates to the American Medical Association be instructed to press for the general adoption of the above principles and proposals by the American Medical Association.

HAROLD R. KURTH
ELMER S. BAGNALL

APPENDIX NO. 4

REMARKS OF DR. MCCANN

By and large, the adoption of these wholly admirable provisions, except for one of them, will place us in a proper and enlightened position toward the Government and the public.

I question the propriety of Proposal No. 4, page 2, lines 5, 6, 7 and 8, which by description of a consumer co-operative mechanism and by use of the word "encourage" in line 8 would maneuver us into what is tantamount to public approval of the consumer co-operative movement. I think we should take some stand concerning it, but not to give encouragement or approval.

The composite memory of any group such as the Council reminds me of an old knife thrown into the corner of a drawer—it gets rusty, loses its edge and does not cut well any longer. However, there are those of us who have served you for ten long years on the firing line in medical economics, whose memories have been kept keenly sharpened while laboring in the field of prepaid medical care.

Why, with Proposal 4 should the Massachusetts Medical Society give approval to the consumer co-operative movement in medicine? With meaningless provisos about advisory medical committees (shades of the Wagner-Murray-Dingell Bill) our profession would be subordinated in such organizations to the bargain-seeking propensities and controls of the lay consumer groups on their own strict terms, or to self-appointed medical managers who probably would be less desirable to bargain with.

The consumer co-operative record is not beyond scrutiny. Their philosophy is essentially that of socialism, although called euphemistically economic democracy, with the organized consumer group dominating and controlling the private medical entrepreneur directly rather than indirectly

through governmental agencies. Their record is not unimpeachable. Their business projects are strewn with the story of use of all the devices ascribed to *laissez-faire* capitalism: price-cutting, tie-in-sales, misrepresentation, monopoly practices—by putting private enterprise out of business. They have used monopoly to break monopoly and then continue themselves to monopolize.

The co-operative's achievements on health matters should be carefully scrutinized.

The White Cross of Massachusetts, after much fanfare and publicity, enrolled a few thousand subscribers, paid doctors 13 cents on the dollar, and then folded up because their fly-white idealists had left for the wars. What the color was of the other boys who went to wars, or of us who stayed behind, I have never found out. Several leaders of this defunct White Cross are on public record in support of compulsory health insurance. One should watch this trend as the record unfolds.

The Group Health Co-operative of Washington, D. C., after many long years finally reports an enrollment of the magnificent total of 24,000 subscribers; there is available their growing list of exclusions and restrictions of services; there is the record of continued use of it by those in the most satisfactory income brackets. A post-mortem examination in this case when it comes will be an interesting study on the anatomy of failure. Of course, under the leadership of Harry Becker, of which more later, they will support compulsory health insurance.

In New York City with the help of considerable endowment, HIP for the moment has had some measure of success under Dr. Dean Clark, who recently came to our hospitable shores, and who, while in the Public Health Service, is said on qualified authority to have been quite sympathetic to compulsory health insurance.

The small co-operative at Elk City, Oklahoma, under Dr. Shadid, is shown by accountant studies to be kept solvent in large measure by the payment for service in the traditional manner, by large numbers of nonmembers from the surrounding areas who use these facilities. Presumably Dr. Shadid and Harry Becker, incorporators and directors of the Co-operative Health Federation of America, subscribed to the unanimously adopted resolution from the parent organization, the Co-operative League of the United States of America, which was presented by a Mr. Hansen to a Congressional Committee September 9-11, 1946. The resolution read in part:

To this end it supports nationwide health insurance under public auspices, provided that any proposed government action in this field provided for the continued expansion of volunteer co-operative health and medical care plans—and the making of Federal loans to consumer sponsored groups for hospitals, clinics and equipment.

The whole medical co-operative philosophy and movement seems to have stemmed from Michael Davis, the presiding genius over the drive for compulsory health insurance from his lesser shadow, veterinarian Nathan Sinae, who aided and abetted the effort to install compulsory health insurance in Hawaii before it should achieve statehood, from Kingsley and Boas, who currently seem to be striving for control of a segment of the New York Medical Society with extravagant promises of things to come—and who of course support compulsory health insurance, and from a charming feminine agent of a Detroit automobile union, who a few years ago challenged me with the startling and arresting words spoken in a strange, unrecognizable, guttural accent, not indigenous to any part of America, at a conference in Ann Arbor sponsored by Michael Davis and his veterinarian Nathan Sinae, "How dare you talk such individualism when we all know that America and the rest of the world is going collectivist!"

As a physician steeped with some others in a modest but real achievement in construction of a multi-million dollar prepayment enterprise, as one who was trained in group medical practice, as one who has practiced both on a group and an individual basis as one who has studied and written medical care contracts based on sound actuarial and labor-management-professional background, I charge that it is time to discredit the unrealistic, fantastic, ideologic shibboleth of the co-operatives that all at once we must throw together, as a blanket to cover the face of our diversified America, the three debatable facets of current medical

mittee and ordered to make restitution to the patient. This case is of interest because it is a repetition of a similar episode in which he was concerned a few years ago. The case is placed on file pending his future conduct.

In the cases of fellow against fellow, all but one of those accused were found guilty, reprimanded by the committee and requested to apologize to the offended brother. These cases were considered closed. In the remaining case, the offending fellow, while not found actually guilty of any infraction of our code of ethics, was adjudged guilty of conduct unbecoming a gentleman and a member of the Massachusetts Medical Society. A letter of severe admonition was sent to him, and his case was placed on file pending his future conduct.

The requests for information regarding ethical procedure varied from information concerning advertising, procedure in appearances in court and also procedures that involved public relations. In general, the advice was given by the chairman and approved by the Committee at the following meeting.

In furtherance of the interest shown by the Society in better public relations between the laity, the press and the medical society, every request for advice on matters pertaining thereto has been given special consideration by the Committee on Ethics and Discipline.

It was with that thought in mind that the Committee approved of the code of ethical conduct sponsored by the Eye and Ear Infirmary of the Massachusetts General Hospital, recently. The Council, at its meeting on February 2, 1949, returned approval of the code to the committee for reconsideration. This matter was discussed at the meeting of the Committee on Ethics and Discipline on February 16, and the committee unanimously reaffirmed its approval of the code of the Eye and Ear Infirmary as printed on page 2 of the circular of advance information to councilors, in advance of the Council meeting on February 2, 1949.

WILLIAM J. BRICKLEY
ARCHIBALD R. GARDNER
FRED R. JOUETT
ALLEN G. RICE
RALPH R. STRATTON, *Chairman*

APPENDIX NO 11

COMMITTEE ON MEDICAL EDUCATION

In accordance with your request, the Committee on Medical Education has communicated with the deans of the three medical schools in Boston and asked them to nominate a fourth-year student to receive the Massachusetts Medical Society prize.

We requested the deans to nominate a student "who best exemplifies those intangible qualities which serve to designate him as the good physician."

The nominations from the deans were as follows:

Boston University — Sylvan B. Baer
Harvard University — Henry S. Harvey
Tufts College — William H. Ellswood

The Committee, therefore, recommends that these nominations be seconded and approved.

JAMES M. FAULKNER
GEORGE D. HENDERSON
ISAAC R. JAVELSON
ROBERT I. MONROE
CHESTER S. KEEFER, *Chairman*

APPENDIX NO 12

ADVISORY SUBCOMMITTEE ON MEDICAL EDUCATION

The following letter from Herbert I. Harris, M.D., and a mimeographed copy of a progress report to the membership of the Massachusetts Society of Clinical Psychologists

from the committee on licensing and certificates of psychologists was referred to this subcommittee for consideration.

Dr. H. Quimby Gallupe
Secretary, Massachusetts Medical Society
8 Fenway
Boston, Massachusetts

Dear Dr. Gallupe:

I enclose for your consideration a progress report of the Massachusetts Society of Clinical Psychologists which is self-explanatory.

It has occurred to me that the present-day interest in the activities of clinical psychologists is such that our Society should be very much aware of what the ethical clinical psychologists are attempting to accomplish in obtaining certification. All those ethical clinical psychologists with whom I have had occasion to talk are agreed that they desire to (a) prohibit the private practice of psychotherapy by clinical psychologists and (b) when clinical psychologists attempt psychotherapy, to insure that adequate psychiatric and medical safeguards and provisions have been provided. You will notice that in this progress report no mention of the exact nature of what the clinical psychologists plan to do in practice is set forth.

It seems to me that the Medical Society would be of considerable help to the ethical clinical psychologists in making sure that a fairly watertight certification law be established, in such fashion that the measures I have outlined above will be included, and that clinical psychologists who are ethical and do wish to work with and under the supervision of psychiatrists have that opportunity.

I am sure you are aware of the fact that many emotional disorders which independent clinical psychologists might attempt to treat often mask an underlying physical disorder, which can on occasion be extremely grave.

I should very much appreciate your views on this entire matter and stand ready to be of any assistance I can to your Legal Committee.

(Signed) HERBERT I. HARRIS, M.D.

20 Lowell Street
Cambridge, Massachusetts

An analysis of the preliminary report shows that 70 per cent of the members of the Massachusetts Society of Clinical Psychologists voted for certification of clinical psychologists by this state on a state level. They are fully aware of the necessity of high standards for such certification and the desirability of uniform legislation in the various states.

From other data available to this subcommittee it appears that the states of Virginia and Connecticut are certifying clinical psychologists and all psychologists respectively. Recently Kentucky passed a law, but because of certain ambiguities in it, it is not certain whether the law provides for certification or licensing of clinical psychologists. Legislation along these lines is pending in New Jersey and the District of Columbia. An attempt is now being made in Virginia to amend the law in favor of licensing clinical psychologists.

It becomes obvious that uniform legislation in all states is impossible, and therefore the standards of training and experience may vary a great deal in the various states.

For approximately two years committees of at least two national psychiatric societies have been deliberating upon the relation between psychiatrists and psychologists in general and clinical psychologists in particular. These committees are likewise considering ways and means to certify or license clinical psychologists on a national basis. To the best of our knowledge no constructive proposals have been made so far. In the meantime, as mentioned above, three states have passed laws to certify or license clinical psychologists and one other state and the District of Columbia are contemplating similar legislation.

Within the framework of the Council on Medical Education of the American Medical Association there are well established precedents for certification, on a national basis, of medical specialties and various other professions allied to the practice of medicine. Such boards of certification exist for surgery, internal medicine, neurology, psychiatry and so forth and for medical technologists, x-ray technicians

similar bills for Hospital Construction, (3) HR 1779 Scholarship Loans to Medical Students, provided the enactment was placed under the Surgeon General of the Public Health Service instead of the Department of Education, and (4) HR 12 and similar bills for a National Science Foundation. It was considered that the several bills relating to cancer, arthritis, and multiple sclerosis could be best handled under a National Science Foundation rather than enacted individually.

It was voted to oppose (1) S 5 and all bills dealing with compulsory health insurance, (2) HR 1512 Chiropractors in Veterans Administration, and (3) HR 1570 Health of School Children in its present form. In regard to establishing a Secretary of Health, Education, and Security (HR 184 and HR 782) it was considered that a single secretary of health as advocated by the American Medical Association was preferable, but, if this goal proved unobtainable, HR 184 was favored provided that the under-secretary of health was a physician, and HR 782 was opposed.

DAVID L. BELDING
VLADO A. GETTING
CHARLES G. HAYDEN
DONALD MUNRO
AUGUSTUS THORNDIKE
ELMER S. BAGNALL, *Chairman*

APPENDIX NO 8

COMMITTEE ON PUBLICATIONS

The Committee wishes to report on the publication of *The New England Journal of Medicine* for the year 1948. The year was marked in all parts of the country by difficulties in the publication of medical journals. Costs have increased, and the revenue from advertising decreased. A majority of the state journals suffered a drop in income from advertisements procured through the Cooperative Medical Advertising Bureau of Chicago. *The New England Journal of Medicine*, however, experienced an increase of 23.8 per cent from this source. The cost of paper rose from \$11.55 per cwt to \$12.60. A new contract for paper at this rate was signed in September, with assurance of benefit of any drop in the general price of paper. The printing contract for 1949 was renewed at the 1948 rate, subject to renegotiation in the event of another increase in printers' wages.

General expenses for 1948 were \$269,018 — an increase of \$28,388 over 1947. The Pension Fund and Social Security taxes account for approximately \$6500 of this amount — and the fact that there were 53 publication dates in 1948 in contrast to the usual 52 added \$3500 to the cost of publication.

Revenue in 1948 was \$267,101 (in addition to which \$5000 was received from the Society) — an increase of \$27,553 over 1947. The net loss for the year 1948 was \$1,916.18.

The total circulation as of the end of December, 1948, was 24,770. The breakdown of this figure is as follows:

Regular subscribers	14,266
Student subscribers	3,725
Massachusetts Medical Society	5,942
New Hampshire Medical Society, once a-month	292
New Hampshire Medical Society "regular"	223
Exchanges	193
Complimentary	59
Advertisers	70
Total	24,770

During the year 1948 the Editorial Board considered 352 manuscripts, of which 170, or 48 per cent, were accepted. This was 46 more manuscripts than in 1947, when 64 per cent were accepted. This indicates a healthy condition and allows greater discrimination in the selection of articles for publication.

The accounts for the year have been audited by Hartshorn and Walter, and a copy of their report is on file in the Treasurer's office. An abstract of the report is appended.

Because of the uncertainty in costs of publication, the Committee requested an appropriation from the Society of \$10,000 for the year 1949, which was included in the budget adopted by the Council at its meeting on February 2, 1949.

Dr. Garland has now been editor of the *Journal* for a full year. His conduct of its affairs has more than justified the confidence in him that was felt at the time of his appointment and augurs well for the future.

The secretary of the Society informs us that there is urgent need for a new Directory. Money for its publication was included in the budget adopted by the Council on February 2, 1949. We recommend that the Council order the publication of a Directory of the Officers and Fellows.

As you will see from the program of this meeting, the Shattuck Lecture will be delivered by Dr. Paul Dudley White, of Boston.

OLIVER COPE
JOHN FALLON
JAMES P. O'HARE
CONRAD WESSELHOFF
RICHARD M. SMITH, *Chairman*

ABSTRACT OF AUDITOR'S REPORT

Expenses	
Publication of <i>Journal</i>	\$183,994.93
Publication of reprints	12,282.46
Office and other salaries	40,547.03
Commissions fees etc.	16,828.42
Office and sundry expense	8,863.66
Pension fund	3,491.10
Social Security taxes	3,008.56
Total	\$269,018.06
Revenue	
Advertising	\$144,480.65
Engraving	595.70
Reprints	11,882.18
Subscriptions (other than M.M.S.)	107,264.87
Miscellaneous	2,878.57
Total	\$267,101.97
Net loss to Massachusetts Medical Society	\$1,916.18

APPENDIX NO 9

COMMITTEE ON ARRANGEMENTS

The program that the Committee presents for the annual meeting is essentially its final report, since it represents the results of our work during the past year.

It is gratifying that so many of our members from the central and western parts of the State have consented to participate in the scientific program. To all these gentlemen, as well as to those who are coming to us from a distance, the Committee extends its thanks.

We again acknowledge the co-operation of the Worcester District Medical Society, whose attention to innumerable details of arrangement that do not appear on the surface but are essential for success has been of inestimable help.

Members of the Society are reminded that the commercial exhibits are the principal source of income for the annual meetings and are urged to visit them frequently.

FRANKLIN G. BALCH, JR.
GORDON DONALDSON
ALBERT EHRENFRIED
JOHN W. NORCROSS
HAROLD G. GIDDINGS, *Chairman*

APPENDIX NO 10

COMMITTEE ON ETHICS AND DISCIPLINE

The "deadline" for submission of the annual report of the Committee on Ethics and Discipline necessitates an incomplete summary of our labors. At the present time, 3 cases of a rather serious nature are being investigated, formal action to be taken later.

The work of the Committee during the year has been concerned with the usual list of complaints against doctors for suspected improper treatment of cases, complaints of fellow against fellow of violation of the code of ethics and requests for guidance in ethical procedure. Of the complaints against fellows by laymen, all but one was decided in favor of the fellow concerned. In this isolated case, the fellow was found guilty of unethical conduct, was reprimanded by the Com-

of Nutrition in Health and recommends that greater emphasis be placed on education in this subject on the undergraduate and graduate medical levels." It is desired that this motion be brought to the attention of the Council for its information.

After considerable and prolonged discussion, the Committee adopted a motion as follows:

It is the opinion of the Committee that pilot clinics should be held in pivotal localities throughout the State to offer, on a voluntary basis, health examinations under the auspices of district medical societies in co-operation with the community hospital and other interested groups. The findings of these examinations, it is recommended, would be referred to the family physician. This committee further recommends that a subcommittee of the Committee on Public Health be appointed to carry out this program, that this subcommittee be made up of one representative from each district and that this subcommittee have power to act. It is the desire of this committee that this motion be presented to the Council for action at the next meeting.

The Committee also recommends that the Council adopt the following resolution: "That positive efforts toward the establishment of local health unions and health centers be actively supported by the individual members of the Massachusetts Medical Society."

The Committee also passed the following resolution: "Whereas the Massachusetts Medical Society has already approved an attempt to find the undiagnosed diabetic patients of the Commonwealth and bring them under treatment, and whereas representatives of a large number of industries in the state have expressed a desire to co-operate with efforts directed at the discovery of latent diabetes in order to secure early treatment, be it resolved that the Council of the Massachusetts Medical Society recommend suitable action by the officers and committees of the district medical societies to carry out such programs aimed at the discovery of diabetes in the community consistent with the Diabetes Detection Program and Diabetes Week sponsored by the American Diabetes Association."

It is requested that you bring this resolution to the attention of the Council for action. It is our understanding that a similar resolution will be adopted for Council action by the Committee on Industrial Medicine and by the Committee on Diabetes. We believe it is Dr. Root's desire that this resolution be presented to the Council as a joint resolve of the three committees.

JOHN J. POUTAS
WARREN R. Sisson
LAWRENCE J. SMITH
CONRAD WESSELHOEFF
ROY J. WARD, *Chairman*

APPENDIX NO 14

HEALTH-PROTECTION CLINICS

It is the desire of all voluntary health agencies of the medical, dental, nursing and hospital professions, of the hospitals and of the official health agencies to make available to all people every essential diagnostic, therapeutic and preventive measure of high quality. In recent years various screening techniques have been made available for determining the probable presence or absence of a certain disease, such as diabetes, cancer, syphilis or tuberculosis.

Health agencies have been screening the public through clinics designed primarily for the application of one or, at the most, two of these procedures. It is our opinion that we are not making available to as many of the public as possible the composite benefits of all the screening techniques applied at a single visit. It is possible to make these screening techniques available as well as a reasonably good history and physical examination in a single visit to a health-protection clinic. The application of these screening devices in a single visit would not be subject to the same error that is now inherent in most of our screening programs — namely, that we screen the patient for one or more types of illness, thereby giving him a false sense of security in believing that

he may be free from all other illnesses. This clinic would screen be patient for all illnesses for which we have an acceptable technique and, in addition, give him the benefit of having a history taken, a physical examination and a personal conference with a physician concerning further steps that he should take to safeguard his health.

Many voluntary health agencies, the professions engaged in the healing arts, voluntary hospitals and public-spirited citizens have become concerned about arguments raised by the proponents of socialized medicine that many people are not afforded proper medical care. The availability of these health-protection clinics would, in our opinion, provide an opportunity for private enterprise in co-operation with the Department of Public Health to make available to meet this apparent need of people who cannot otherwise afford to obtain health protection for themselves.

These clinics are for the purpose of finding the presence or absence of certain major illnesses that are some of the leading causes of death. The objective of the clinic is to examine persons referred by the family physician, clinics or other social agencies, by applying screening procedures, giving a physical examination and performing certain laboratory tests that would assure the person of his apparent good health. The clinic visit would be terminated by a personal conference with a physician who would instruct him about the proper follow-up study, including visits to his family physician or clinic if he cannot afford the former and obtaining the name of a physician to whom the final report will be sent. For certain health-protection purposes such as dietary supervision for overweight or in case of diabetes, follow-up services would be offered at the request of the family physician, or if there were no family physician at the request of the clinic or other group caring for the patient.

This co-operative project between the medical profession, the voluntary hospitals, the cancer, tuberculosis, diabetic and heart voluntary associations and others would depend upon the following factors:

The organization of a central guiding committee, which would elect an administrator who would be responsible for the operation of the program.

Mutual sponsorship of such a program by the various groups who would participate both financially and in the promotion of the program.

The development of a plan for the opening of a demonstration health-protection clinic, which might be used as a guide for developing others throughout the Commonwealth.

The establishment of a plan and budget for the maintenance of this clinic by the sponsoring agencies under the direction of the administrator whom they would select.

Direction of the public-relations program by the administrator and joint participation by all the agencies concerned. (In order to be effective, the program must be well publicized to the professions concerned as well as to the public.)

It is suggested that no charge be made for services rendered except that persons who are processed through the clinic might, if they wish, contribute to the support of the clinic any amount that they were able to pay up to the actual cost of the services rendered. All such funds would accrue to the advancement of the clinic and not to the participating agencies sponsoring it.

The Department of Public Health would not control this clinic in any fashion other than by licensing, but would be one of the sponsoring agencies.

The data collected at the clinic should be available to all the sponsoring agencies for scientific analysis but the identity of patients processed in the clinic would be kept confidential and not made available to any of the sponsoring agencies.

It is the objective of the Department to present this proposed health-protection clinic to a group of agencies and individuals in the Commonwealth who may be interested in making available to the people of the Commonwealth these services. We believe that through these services which would include a history, a physical examination, an x-ray film of the chest, a blood test and a Papanicolaou test for vaginal smears, we should be able to screen the presence of the major killers — namely, heart disease, cancer, diabetes, tuberculosis, nephritis and

medical librarians and others. They maintain high standards of education, training and experience for certification in their respective fields. A similar technic for certification of clinical psychologists would establish a uniformly high standard throughout the country. We suggest that such board should be under the guidance of the American Board of Neurology and Psychiatry and function with the approval of the Council on Medical Education of the American Medical Association.

We therefore recommend that

1 Certification of clinical psychologists by the American Board of Neurology and Psychiatry be approved. Certification by the State is disapproved.

2 Licensure by the State to practice clinical psychology is not supported by us at this time.

One member of this subcommittee, Dr. George E. Gardner, dissented from the above recommendations and will submit an alternate recommendation.

RAYMOND H. GOODALE
WILLIAM A. HINTON
C. GUY LANE
DONALD A. NICKERSON
AUGUSTUS THORNDIKE
I. R. JANNESEN, *Chairman*

MINORITY REPORT OF ADVISORY SUBCOMMITTEE ON MEDICAL EDUCATION

This problem of licensure and certification is a very complex one, and I might say that it is one that at the present moment is engaging the attention of numerous professional committees at the national level. For example:

1 There is a committee of the American Psychiatric Association called the Committee on the Relation of Psychiatry with Psychology. This committee at the present time is wrestling with this very problem of the training of the clinical psychologist, the function, with a view of emerging eventually with some suggestions regarding the ticklish problem of certification or licensure. In doing this it is working in close collaboration—in joint committee meetings, to be exact—with the Committee of the American Psychological Association on the relation of psychology with psychiatry. The memberships of both these committees are representative of the two disciplines, and the results of their work are being awaited by both groups.

2 There is also a committee at the national level—namely, the Committee on Clinical Psychology of the Group for the Advancement of Psychiatry—that is endeavoring to establish in collaboration with representatives from the American Psychological Association some fixed standards of training, Ph.D. requirements, experience and supervision and so forth that will be satisfactory not only to the psychiatrists but also to the psychologists. This committee is turning its attention to the very pressing problem of licensure and certification and is also not out of touch with the work of the committees noted above.

3 The psychologists themselves, through the recent establishment of their Board of Examiners for Professional Psychologists, have put through and are now enforcing rigorous standards for certification as a diplomate in clinical psychology. This in itself all assume to be a step in the right direction toward a national worthwhile plan.

4 And, finally, only yesterday Dr. Dael Wolfe, executive secretary of the American Psychological Association in Washington, through communications to me by way of Dr. William Menninger, president of the American Psychiatric Association, has called for a representative from psychiatry, together with representatives from the other disciplines involved, to meet together in a few weeks to definitely take steps to establish a uniform national procedure of certification of clinical psychologists—all psychologists in whatever capacity they may work directly with the public.

I have gone into the various steps taken by these various interested bodies of professional people so that it will be clear that there is at present much work being done toward a solution of this very important problem, and

it seems to me that it would be much less precipitate if we at the local level should await the results and possibly the accepted program of the people working in the fields most affected. I say we should do this rather than put forth a statement that we favor any such thing as certification by the American Medical Association, its Council, or the Board of Neurology and Psychiatry and so forth. This whole problem of the function and role of the clinical psychologist is too complex to be settled merely by stating that these people (over 5000 of them as a matter of fact—most of whom have Ph.D. degrees) are to be considered “adjuncts to the medical profession” and thus to be classified and certified as technologists, technicians and librarians. The work of the psychiatrists on the above committees during the past two and a half years has convinced them that no such simple solution would suffice.

Therefore, in the light of the above, I suggest, that our committee go on record as stating:

In view of the fact that well accredited bodies and committees of psychiatrists sponsored by their national professional organizations, working in close collaboration with representatives of the American Psychological Association, are at this time endeavoring to establish a nation-wide policy of certification and licensure of clinical psychologists, it is the opinion of this committee that any and all such steps toward licensure and certification at the state level in Massachusetts should await the results and suggestions relating to licensure and certification on a national level. While awaiting these programs, we are opposed to licensure and certification at the state level, feeling that such a plan would be premature, or inadequately formulated, or both.

I hope that some of these data will help clarify the issues for us, but if you and the rest of the committee feel that you do wish to go on record in the matter as outlined on Page 2 of your report referable to certification, may I ask you if you will omit my name from those of the committee who agree with these proposals. If my name were to be forwarded at all in connection with such proposals, I would like to have you list me as “dissenting,” and if possible for the reasons outlined above.

GEORGE E. GARDNER

APPENDIX NO. 13

COMMITTEE ON PUBLIC HEALTH

The Public Health Committee at its November 15 meeting heard a presentation by Dr. Monroe of certain problems with respect to the care of the aged. The Committee at its March 2 meeting endorsed once again the program of Dr. Monroe and voted that this endorsement be brought to the attention of the Council. Dr. Monroe's discussion before the Committee was as follows. He pointed out that of the approximately 100,000 persons in this state over age sixty-five, a third were independent and working, a third were independent owing to insurance, and a third were dependent upon charity of one type or another, or some form of social security. He stressed the need for improving the professional standards in so-called nursing homes and boarding homes. He described to the Committee his model home for the aged, which would include such services as employment, rehabilitation, teaching, recreation, preventive medicine, and even the provision of part-time house-keeping to the aged persons in their own homes.

At its November 15 meeting the Committee also adopted the following motion, which, it voted at its March 2 meeting, should be brought to the attention of the Council: “This committee endorses in principle the limited investigation of the use of BCG vaccine in tuberculosis contact families in certain districts of Boston by the Tuberculosis Division of the Boston Health Department in collaboration with the U. S. Public Health Service and the State Health Department subject to the approval of the Massachusetts State Department of Health.”

At its March 2 meeting the Committee adopted the following motion: “This Committee recognizes the importance

or much of their time to industrial medicine. The qualifications for membership are the same as those in the parent association. Here again are many physicians doing some industrial medicine who are not members of the Conference.

The Boston Branch of the New England Association of Industrial Nurses is a component society of the American Association of Industrial Nurses, a very flourishing and active though relatively young organization designed for the development and professional advancement of nurses working in industry. Some of our colleges that conduct schools of nursing include industrial nursing as an important part of the curriculum and provide in-plant training.

It is apparent, therefore, that industrial medicine and industrial nursing have become an important department in both professions.

A recent survey made by the Division of Occupational Hygiene of the Commonwealth of Massachusetts in 654 industries employing 398,800 persons reveals the following information:

Number of physicians employed full time	19
Number of physicians employed part time	159
Number of physicians employed on call	416
Total	594
Number of nurses	829

As you are not unaware, organized labor has become concerned about the health of its members and many of them are now including medical service in their negotiable contracts. That is true especially in the United Mine Workers organizations, the Garment Workers Union, the power companies, the automobile industries and others.

As previously reported, the seventy-ninth Congress enacted legislation establishing a Federal Employees Health Service which is a further recognition of the importance of industrial medicine. Units have been recommended for Boston by the United States Public Health Service but have not yet been organized.

Stimulated by workmen's compensation legislation for industrial accident and diseases to some degree the large industries and businesses throughout the Commonwealth are now providing a quite satisfactory medical service or health-maintenance program for their employees. As in every phase of medical practice, there is room for improvement in some of these services especially when employed nurses are not under responsible medical supervision.

It has been very difficult to introduce worthwhile health-maintenance programs in small industries. There are several reasons for this, among them fear of the cost, the uncertain economic outlook in the country, the uncertain demands from labor and a lack of medical men properly trained in industrial medicine. We are advised by the American Medical Association, Council of Industrial Health that this condition exists all over the country and presents a challenge that nobody has yet been able to meet successfully. It will continue to be a problem for the earnest endeavor of this committee to solve with the help of other interested groups.

This committee wishes to recommend the adoption by the Council of the resolution submitted by the chairman of the Committee on Diabetes, which is a joint resolution by that Committee, the Committee on Public Health and the Committee on Industrial Health, for the detection of the patients with unrecognized diabetes in industry and in the community.

This committee also wishes to present the following resolution:

Whereas, industrial medicine has become an important part of the American Medical Association's Program for the Advancement of Medicine and Public Health and is being favorably considered by the Association for specialty status,

Be it resolved, that the Council of the Massachusetts Medical Society establish a section on industrial health so that this phase of practice may participate in the annual meetings of the Society with the other sections of the Society.

JOSEPH C. AUB
LOUIS R. DANIELS
JOHN G. DOWNING
HAROLD R. KURTZ
FREDERICK N. MANLEY
HENRY C. MARBLE
DANIEL L. LANCZ, *Chairman*

APPENDIX NO 18

COMMITTEE TO MEET WITH THE MASSACHUSETTS HOSPITAL ASSOCIATION

Last December, in response to many inquiries at the office of the Secretary as to the acceptance and degree of success of the Gallupe Plan previously approved by the Society, a questionnaire was sent each hospital in the Commonwealth through the office of each district secretary. All hospitals were included whether approved or not, private or public, large or small. The questions asked were:

1. Did or did not co-operate in the promotion of the Gallupe Plan?
2. To what extent?
3. How has it worked?
4. Have you any physicians on either the regular, courtesy, or supervised courtesy staffs who are graduates of unapproved schools?
5. How many?
6. How many have you accepted under the Gallupe Plan?
7. If nothing was done, why not?
8. Remarks.

Replies were received from 55 hospitals in 15 districts having a total bed capacity of approximately 7800. No state, federal or teaching hospital associated with a medical school participated. Twenty-seven, or approximately 50 per cent, have replied that they were co-operating in the promotion of the Gallupe Plan, and reported a total of 194 graduates of unapproved medical schools on their supervised courtesy staffs. All reported that the plan was working "well or satisfactorily." None reported unfavorably. Some complained of the time and effort required of the staff men who did the supervising. In some cases certain men have been promoted to the regular courtesy staff on the basis of their work and interest. Thirty-six hospitals reported a total of 270 graduates of unapproved schools on their combined staffs—usually the supervised courtesy staff. The largest number reported by any one hospital was 68, whereas others reported 27, 15, 15, 15 and 15 respectively.

The reasons most commonly given for not participating in the operation of the Gallupe Plan were staff regulations, scarcity of beds, which prevented acceptance of all physicians of approved schools who had made application, many small hospitals in rural areas reported no demand from graduates of unapproved schools.

Even though the percentage of questionnaires returned is small, from the information given, by the hospitals where the plan is in operation, it appears that it has real merit, that the men selected have greatly appreciated the opportunity given them, and that the postgraduate teaching from clinics, staff meetings and supervised care of patients has helped make better physicians of these men who graduated from unapproved medical schools. We hope the plan will be adopted more generally.

EDWARD A. ADAMS
EDWIN D. GARDNER
FREDERIC HAGLER
JUSTIN E. HAYES
LELAND S. MCKITTRICK
DONALD A. NICKERSON
NICHOLAS S. SCARCELLO
ALBERT E. PARKHURST, *Chairman*

APPENDIX NO 19

COMMITTEE ON MATERNAL WELFARE

During 1948 two meetings were held on February 17 and November 16. The following members of the Committee were present at one or both of these meetings: Raymond S. Titus, M.D., Arthur F. G. Edgelow, M.D., Richard P. MacKnight, M.D., Robert L. DeNormandie, M.D., and David D. Rutstein, M.D., Arthur Hertig, M.D., and Miss Alice G. MacKinnon, R.N., were guests.

In co-operation with the Committee on Maternal and Child Welfare of the Department of Public Health, Common-

hypertension — and other conditions that may lead to serious protracted illness, or disability, or even death

VLADO A. GETTING
Massachusetts Commissioner of Public Health

APPENDIX NO 15

COMMITTEE ON MEDICAL DEFENSE

Malpractice cases carried over from 1947	9
Cases disposed of in 1948	5
New cases in 1948	6
Cases pending as of January 1 1949	10
Legal expenses 1948	\$3,730 00
Other expenses	None

The unusually large expenditure resulted from 2 cases that together cost \$2184 33 (\$1186 76 and \$997 57). The first took a month in Superior Court, resulted in a verdict for the doctor and has been carried to the Supreme Court on appeal by the plaintiff. The second was primarily defended by an insurance-company attorney, but the Society also filed its own brief because of the importance of the questions involved. Trial resulted in a verdict against the doctor, but the Society was reassured by the court's statement that "Nothing contained herein need cause anxiety to an honest physician who administers narcotics to a patient in accordance with the prevailing standards of medical practice."

Although it is unlikely that such important demands will be made on this committee in 1949, it has still been thought advisable to increase the budget from \$1500 00 to \$2000 00 in order to give the treasurer a fairer picture of what can happen. This has been done, and it is the hope of the Committee that the increase will be returned unused at the end of the year.

EDWIN D. GARDNER
CHARLES J. KICHAHAM
JOHN E. MORAN
WILLIAM R. MORRISON
HORATIO ROGERS, *Chairman*

APPENDIX NO 16

COMMITTEE ON SOCIETY HEADQUARTERS

It is obvious that the present quarters of the Massachusetts Medical Society are not adequate for its purposes, and this committee has failed to obtain the building next to the Boston Medical Library.

There is an opportunity for the Massachusetts Medical Society to unite with the Boston Museum of Science, which has recently bought six acres of land in Boston on which to construct a new museum. The museum will include a planetarium and a Hall of Man.

On March 25, 1949, a meeting of the Committee on Society Headquarters was held. Present at this meeting, besides the members of the Committee, were Dr. Reardon, president, Dr. Gallupe, secretary, and Mr. Robert Boyd, executive secretary of the Massachusetts Medical Society. At this meeting, it was decided to ask the Executive Council of the Society for authority to explore the possibility of obtaining headquarters for the Massachusetts Medical Society, the Boston Medical Library, and the *New England Journal of Medicine* and to report its findings at a future meeting of the Council.

It may be possible, if we find it feasible, to unite with the Boston Museum of Science. This would give the Massachusetts Medical Society the opportunity to establish better public relations and to enhance the value of the doctor to his patient.

ALBERT A. HORNOR
DWIGHT O'HARA
WALTER G. PHIPPEN
GEORGE L. STEELE
FRANK R. OBER, *Chairman*

APPENDIX NO 17

COMMITTEE ON INDUSTRIAL HEALTH

The inclusion by the American Medical Association in its program for the advancement of medicine and public health of a section devoted to industrial medicine is evidence, in our opinion, of the importance with which the House of Delegates of the Association now regards this specialty and a recognition, at long last, that industrial medicine, once an outcast and later the tolerated stepchild of the profession, has attained full status and dignity because of the indisputably valuable contribution it has made to the health and welfare of the largest segment of the nation's population in peace and in war and by reason of the professional character, integrity and standing of the men who nurtured and developed it over the last quarter of a century and overcame many obstacles by meritorious performance.

Section No 11 of the American Medical Association's program is captioned "Industrial Medicine" and proposes, "Greater emphasis on the program of industrial medicine, with increased safeguards against industrial hazards and prevention of accidents occurring on the highway, home and on the farm."

Of course this program requires the talent and the aid of many ancillary services, of nurses and technicians, safety and mechanical engineers, chemists and physicists and so forth, but all these must be, as in the past, correlated and guided by the physician in industry whose concern is the health and well-being of people at work.

This program also requires the optimum of help and cooperation from the family physician and the surgeon to the end that the disabled worker may be restored to working capacity as fully and as promptly as possible.

It must be perfectly obvious that if our nation is to survive indivisible with liberty and freedom for all and at the same time carry on its back indefinitely more than sixty war-damaged or sick foreign countries it can be done only through sustained and increasing and efficient production of goods and services.

Such an achievement is unlikely in the event of any important breakdown in our nation's industrial health. It is, therefore, the job of industrial medicine working with the public-health and related services at all levels to endeavor to maintain the health of this nation's 60,000,000 working people and their families at a high level.

It should be unnecessary but it may be important to make it crystal clear at this point that industrial medicine is basically preventive medicine or health maintenance, a determined effort to keep well people well, and able and willing to work. Except in areas isolated from good medical care, in emergencies or other necessitous circumstances or legal edict, industrial medicine has no intention or desire to enter into the field of curative medicine.

In recent years our medical schools have taken cognizance of the importance of industrial medicine, and many of them have established postgraduate courses in industrial medicine. Because of its increasing importance it should, however, have its place in the undergraduate curriculum.

At the present time the American Medical Association is giving favorable consideration to recognition of industrial medicine as a specialty equal to surgery, internal medicine, neurology and so forth. To this end fellowships and residencies in industrial medicine are being established. The American Association of Industrial Physicians and Surgeons has sponsored such a fellowship at the University of Pittsburgh, and General Motors Corporation has established several in-plant residencies for training.

The American Association of Industrial Physicians and Surgeons now comprises upward of 2000 members, nearly all in this country. These are physicians who must devote full time or at least 50 per cent of their time to industrial medicine, must have so performed for five years and must belong to their local medical society to qualify for membership.

Across the country many more physicians engaged in industrial work full time or part time who are not members of the Association are unable to meet the qualifications or from choice.

The local component society of the national association, the New England Conference of Industrial Physicians and Surgeons, includes approximately 150 physicians in this area, chiefly in Massachusetts and Rhode Island, who devote all

or much of their time to industrial medicine. The qualifications for membership are the same as those in the parent association. Here again are many physicians doing some industrial medicine who are not members of the Conference.

The Boston Branch of the New England Association of Industrial Nurses is a component society of the American Association of Industrial Nurses, a very flourishing and active though relatively young organization designed for the development and professional advancement of nurses working in industry. Some of our colleges that conduct schools of nursing include industrial nursing as an important part of the curriculum and provide in-plant training.

It is apparent, therefore, that industrial medicine and industrial nursing have become an important department in both professions.

A recent survey made by the Division of Occupational Hygiene of the Commonwealth of Massachusetts in 654 industries employing 398,800 persons reveals the following information:

Number of physicians employed full time	19
Number of physicians employed part time	159
Number of physicians employed on call	416
Total	594
Number of nurses	829

As you are not unaware, organized labor has become concerned about the health of its members and many of them are now including medical service in their negotiable contracts. That is true especially in the United Mine Workers organizations, the Garment Workers Union, the power companies, the automobile industries and others.

As previously reported, the seventy-ninth Congress enacted legislation establishing a Federal Employees Health Service which is a further recognition of the importance of industrial medicine. Units have been recommended for Boston by the United States Public Health Service but have not yet been organized.

Stimulated by workmen's compensation legislation for industrial accident and diseases to some degree the large industries and businesses throughout the Commonwealth are now providing a quite satisfactory medical service or health-maintenance program for their employees. As in every phase of medical practice, there is room for improvement in some of these services especially when employed nurses are not under responsible medical supervision.

It has been very difficult to introduce worthwhile health-maintenance programs in small industries. There are several reasons for this, among them fear of the cost, the uncertain economic outlook in the country, the uncertain demands from labor and a lack of medical men properly trained in industrial medicine. We are advised by the American Medical Association, Council of Industrial Health that this condition exists all over the country and presents a challenge that nobody has yet been able to meet successfully. It will continue to be a problem for the earnest endeavor of this committee to solve with the help of other interested groups.

This committee wishes to recommend the adoption by the Council of the resolution submitted by the chairman of the Committee on Diabetes, which is a joint resolution by that Committee, the Committee on Public Health and the Committee on Industrial Health, for the detection of the patients with unrecognized diabetes in industry and in the community.

This committee also wishes to present the following resolution:

Whereas, industrial medicine has become an important part of the American Medical Association's Program for the Advancement of Medicine and Public Health and is being favorably considered by the Association for specialty status,

Be it resolved, that the Council of the Massachusetts Medical Society establish a section on industrial health so that this phase of practice may participate in the annual meetings of the Society with the other sections of the Society.

JOSEPH C. AUB
LOUIS R. DANIELS
JOHN G. DOWLING
HAROLD R. KURTZ
FREDERICK N. MANLEY
HE. FYC. MARBLE
DANIEL L. LYNCH, *Chairman*

APPENDIX NO 18

COMMITTEE TO MEET WITH THE MASSACHUSETTS HOSPITAL ASSOCIATION

Last December, in response to many inquiries at the office of the Secretary as to the acceptance and degree of success of the Gallupe Plan previously approved by the Society, a questionnaire was sent each hospital in the Commonwealth through the office of each district secretary. All hospitals were included whether approved or not, private or public, large or small. The questions asked were:

1. Did or did not co-operate in the promotion of the Gallupe Plan?
2. To what extent?
How has it worked?
Have you any physicians on either the regular, courtesy or supervised courtesy staffs who are graduates of unapproved schools?
3. How many?
6. How many have you accepted under the Gallupe Plan?
7. If nothing was done, why not?
8. Remarks.

Replies were received from 55 hospitals in 15 districts having a total bed capacity of approximately 7800. No state federal or teaching hospital associated with a medical school participated. Twenty-seven, or approximately 50 per cent, have replied that they were co-operating in the promotion of the Gallupe Plan, and reported a total of 194 graduates of unapproved medical schools on their supervised courtesy staffs. All reported that the plan was working well or satisfactorily. None reported unfavorably. Some complained of the time and effort required of the staff men who did the supervising. In some cases certain men have been promoted to the regular courtesy staff on the basis of their work and interest. Thirty-six hospitals reported a total of 270 graduates of unapproved schools on their combined staffs—usually the supervised courtesy staff. The largest number reported by any one hospital was 68, whereas others reported 27, 15, 15, 13 and 13 respectively.

The reasons most commonly given for not participating in the operation of the Gallupe Plan were: staff regulations, scarcity of beds, which prevented acceptance of all physicians of approved schools who had made application, many small hospitals in rural areas reported no demand from graduates of unapproved schools.

Even though the percentage of questionnaires returned is small from the information given, by the hospitals where the plan is in operation, it appears that it has real merit, that the men selected have greatly appreciated the opportunity given them, and that the postgraduate teaching from clinics, staff meetings and supervised care of patients has helped make better physicians of these men who graduated from unapproved medical schools. We hope the plan will be adopted more generally.

EDWARD A. ADAMS
EDWIN D. GARDNER
FREDERIC HAGLER
JUSTIN E. HATES
LELAND S. MCKITTRICK
DONALD A. NICKERSON
NICHOLAS S. SCARCELLO
ALBERT E. PARKHURST, *Chairman*

APPENDIX NO 19

COMMITTEE ON MATERNAL WELFARE

During 1948 two meetings were held on February 17 and November 16. The following members of the Committee were present at one or both of these meetings: Raymond S. Titus, M.D., Arthur F. G. Edgelow, M.D., Richard P. MacKnight, M.D., Robert L. DeNormandie, M.D., and David D. Rutstein, M.D., Arthur Herzog, M.D., and Miss Alice G. MacKinnon, R.N., were guests.

In co-operation with the Committee on Maternal and Child Welfare of the Department of Public Health, Common-

hypertension — and other conditions that may lead to serious protracted illness, or disability, or even death

VLADE A. GETTING
Massachusetts Commissioner of Public Health

APPENDIX NO 15

COMMITTEE ON MEDICAL DEFENSE

Malpractice cases carried over from 1947	9
Cases disposed of in 1948	5
New cases in 1948	6
Cases pending as of January 1 1949	10
Legal expenses, 1948	\$3 730 00
Other expenses	None

The unusually large expenditure resulted from 2 cases that together cost \$2184 33 (\$1186 76 and \$997 57). The first took a month in Superior Court, resulted in a verdict for the doctor and has been carried to the Supreme Court on appeal by the plaintiff. The second was primarily defended by an insurance-company attorney, but the Society also filed its own brief because of the importance of the questions involved. Trial resulted in a verdict against the doctor, but the Society was reassured by the court's statement that "Nothing contained herein need cause anxiety to an honest physician who administers narcotics to a patient in accordance with the prevailing standards of medical practice."

Although it is unlikely that such important demands will be made on this committee in 1949, it has still been thought advisable to increase the budget from \$1500 00 to \$2000 00 in order to give the treasurer a fairer picture of what can happen. This has been done, and it is the hope of the Committee that the increase will be returned unused at the end of the year.

EDWIN D. GARDNER
CHARLES J. KICKHAM
JOHN E. MORAN
WILLIAM R. MORRISON
HORATIO ROGERS, *Chairman*

APPENDIX NO 16

COMMITTEE ON SOCIETY HEADQUARTERS

It is obvious that the present quarters of the Massachusetts Medical Society are not adequate for its purposes, and this committee has failed to obtain the building next to the Boston Medical Library.

There is an opportunity for the Massachusetts Medical Society to unite with the Boston Museum of Science, which has recently bought six acres of land in Boston on which to construct a new museum. The museum will include a planetarium and a Hall of Man.

On March 25, 1949, a meeting of the Committee on Society Headquarters was held. Present at this meeting, besides the members of the Committee, were Dr. Reardon, president, Dr. Gallupe, secretary, and Mr. Robert Boyd, executive secretary of the Massachusetts Medical Society. At this meeting, it was decided to ask the Executive Council of the Society for authority to explore the possibility of obtaining headquarters for the Massachusetts Medical Society, the Boston Medical Library, and the *New England Journal of Medicine* and to report its findings at a future meeting of the Council.

It may be possible, if we find it feasible, to unite with the Boston Museum of Science. This would give the Massachusetts Medical Society the opportunity to establish better public relations and to enhance the value of the doctor to his patient.

ALBERT A. HORNOR
DWIGHT O'HARA
WALTER G. PHIPPEN
GEORGE L. STEELE
FRANK R. OBER, *Chairman*

APPENDIX NO 17

COMMITTEE ON INDUSTRIAL HEALTH

The inclusion by the American Medical Association in its program for the advancement of medicine and public health of a section devoted to industrial medicine is evidence, in our opinion, of the importance with which the House of Delegates of the Association now regards this specialty and a recognition, at long last, that industrial medicine, once an outcast and later the tolerated stepchild of the profession, has attained full status and dignity because of the indisputably valuable contribution it has made to the health and welfare of the largest segment of the nation's population in peace and in war and by reason of the professional character, integrity and standing of the men who nurtured and developed it over the last quarter of a century and overcame many obstacles by meritorious performance.

Section No 11 of the American Medical Association's program is captioned "Industrial Medicine" and proposes, "Greater emphasis on the program of industrial medicine, with increased safeguards against industrial hazards and prevention of accidents occurring on the highway, home and on the farm."

Of course this program requires the talent and the aid of many ancillary services, of nurses and technicians, safety and mechanical engineers, chemists and physicists and so forth, but all these must be, as in the past, correlated and guided by the physician in industry whose concern is the health and well-being of people at work.

This program also requires the optimum of help and co-operation from the family physician and the surgeon to the end that the disabled worker may be restored to working capacity as fully and as promptly as possible.

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Dr Samuel A Robins, reappointment
Dr James C McCann, reappointment
Mr Harold B Leland, reappointment

To hold office until 1951

Mr Everett Thatcher, to replace Dr Eugene Walker, who has resigned

Employee Relations Secretary, Community Chest Springfield, Massachusetts

Mr Wilfred T Connell, to replace Mr Benjamin Hull who has resigned

Business Manager, Boston Photo-Engravers Union No 3, 294 Washington Street, Boston, Massachusetts

HAROLD G GINNINGS
ELLIOTT P JOSLIN
PEIRCE H LEAVITT
GEORGE G SMITH
LELAND S MCKITTRICK, *Chairman*

APPENDIX NO 23

COMMITTEE ON SCHOOL HEALTH

This committee met on March 23, 1949, with Drs Morris, Bagnall, McKay, Garland and MacLachlan present Dr Allan R Cunningham, of the Department of Public Health, was a guest.

Whatever is done by the school physician must be done well. This axiom should be the guide in any program designed for the school physician.

Efforts should be continued to interest district medical societies in appointing a committee on school medical services. A section on school health of the Massachusetts Medical Society, as suggested at the Massachusetts Health Conference, might better accomplish this purpose.

The Committee favors the establishment of full-time, trained community health units as recommended by the special commission established in 1947 to study and investigate certain public-health matters (H 1766) and believes that the development of such units with full-time, trained personnel will necessarily assist in the development of satisfactory school health services.

The Committee believes that health education is a basic need

- a By teachers specially trained in this field
- b By guided health experiences
- c By participation such as is provided by school health council and student health councils
- d By attendance of parents at health examinations

The Committee approves in-service training courses for professional personnel for the purpose of improving school medical services

- a To develop effective teacher-nurse conferences for screening and other purposes
- b Basic psychiatric screening methods should be developed in school physicians to enable them to detect cases in need of special expert attention
- c Courses in school health for physicians, should be sponsored by the Massachusetts Medical Society, in collaboration with the Department of Public Health and the schools of public health

ELMER S BAGNALL
STEWART H CLIFFORD
JOSEPH GARLAND
FLORENCE L MCKAY
KENNETH L MACLACHLAN
THOMAS F REILLY
ERNEST M MORRIS, *Chairman*

APPENDIX NO 24

SUBCOMMITTEE OF THE EXECUTIVE COMMITTEE ON BLUE CROSS-BLUE SHIELD PROBLEMS

The Subcommittee of the Executive Committee on Blue Cross-Blue Shield Problems met at 8 Fenway on Friday, March 25, at 4:00 p m

Your subcommittee was represented at a meeting of the Chairmen of Blue Shield's District Professional Service Committees, Officers of the Massachusetts Medical Society and members of the Blue Shield Board of Directors, held on January 26, 1949, at which the question of charges to limited (over-income) members of Blue Shield was discussed at length. Considerable evidence was presented that fees are not always based on ability to pay. Although it was suggested that charges to limited (over-income) members of Blue Shield be limited to fixed percentages of the basic Blue Shield allowance, this suggestion was discarded, and the Executive Director was instructed to refer cases that could not be resolved in his office to the appropriate Blue Shield District Professional Service Committee. This mechanism is in accordance with the Blue Shield By-Laws as approved by the Council of the Massachusetts Medical Society.

Your subcommittee believes that the unreasonable charges being rendered in certain instances to Blue Shield and non-Blue Shield patients alike are having an adverse effect upon the public-relations efforts of the Massachusetts Medical Society. It is therefore recommended that a subcommittee of the Committee on Public Relations be constituted to investigate the allegation that patients are being charged fees in excess of their ability to pay, and, if such practice exists, to recommend an appropriate remedy.

Because of the severe cut in benefits undertaken on May 1, 1948, Blue Cross now finds itself in the position of being able to liberalize its subscriber contract. To this end it has just completed a series of twenty-one meetings with representatives of subscriber groups throughout the Commonwealth. It is anticipated that in the near future Blue Cross will increase the number of "full-benefit" days from thirty to sixty and the maternity allowance from seven dollars (\$7.00) per day through ten days to a flat seventy dollars (\$70.00) per case.

Your subcommittee has been advised that the formation of a Blue Shield insurance company will in all probability be considered by the American Medical Association House of Delegates in Atlantic City next June. The proposed Blue Shield company would be independent of the Blue Cross company now being organized but would, no doubt, work co-operatively with the Blue Cross company.

Your committee recommends that the Massachusetts Medical Society record itself as favoring the establishment of an independent Blue Shield insurance company to provide Blue Shield coverage for national accounts in areas where coverage is not now available and supplement coverage in areas where existing coverage does not adequately satisfy the reasonable demands of national accounts.

PAUL M BUTTERFIELD
JOHN FALLON
HARVEY A KELLY
JOSEPH C MERRIAM
CHARLES J E KICKHAM, *Chairman*

APPENDIX NO 25

COMMITTEE ON BY-LAWS AND COUNCIL RULES

The Committee met at the Harvard Club on March 23, 1949. Present were Drs Edward P Bagg, Albert A Hornor, Elmer S Bagnall, Daniel B Reardon and H Quimby Gallepe.

In order to enhance the efforts of the Director of Medical Information and Education and in order to bring his work before the Council the Committee unanimously recommends the following amendments to the by-laws of the Society as amended May 25, 1948.

1 Chapter IV, Section 1 eliminate the "and" following the second comma in line 4 and insert after the comma following the word "Society" in line 4 the words "The Director of Medical Information and Education."

2 Add to Chapter VI, Section 8, as amended, the following "He shall be a nonvoting member of all committees of the Society, with the exception of the Committee on Ethics and Discipline. He shall be privileged to distribute the information acquired from these committees with the approval of the respective chairmen."

The committee recommends that it be authorized to publish a new volume containing the Digest, By-Laws, Code of

wealth of Massachusetts, it was decided that a study of maternal mortality should be conducted throughout the entire Commonwealth. Through the efforts of Dr. Florence McKay a sum of money was obtained from the Children's Bureau in Washington to finance this study, which will be directed by Dr. Luke Gillespie and Dr. Arthur Edgelow. It has been proposed that a review of maternal deaths be made during the year, and a representative committee will arrive at a decision whether these deaths were preventable or nonpreventable. Plans will be made to review this material periodically at meetings open to the general medical public.

JAMES M. BATY
ARTHUR F. G. EDGELOW
SAMUEL KIRKWOOD
FLORENCE L. MCKAY
LOUIS E. PHANEUF
RAYMOND S. TITUS
DUNCAN E. REID, *Chairman*

APPENDIX NO. 20

COMMITTEE ON POST-GRADUATE MEDICAL EDUCATION

Attention of the Society is directed to the fact that the work of this committee now includes the New England Post-Graduate Assembly, the directors of various post-graduate exercises carried on throughout the State and the conduct of the Sanders Theater Course.

New England Post-Graduate Assembly

This year the Assembly will meet at the Copley Plaza Hotel on November 9, 10 and 11.

Making full use of past experiences, the organization of various committees from this and other states has been accomplished. By vote of the program committee arrangements have been made to omit the various hospital clinics and in their place to devote a full day to television exercises, both surgical and medical. Other than this note of progress, there is no further report at this time.

Post-Graduate Medical Exercises — Fall and Winter 1948-49

At the outset it should be stated that as a result of a personal survey of the various teaching areas during the summer months, together with certain experiences early in the Fall of 1948, it seemed advisable to all concerned to make certain changes in the teaching framework. As a result, the teaching areas are as follows:

- Area 1 — Pittsfield, North Adams, Great Barrington
- Area 2 — Springfield, Holyoke
- Area 3 — Greenfield, Turners Falls
- Area 4 — Worcester
- Area 5 — Fitchburg, Gardner, Leominster
- Area 6 — Lowell
- Area 7 — Lawrence, Haverhill, Newburyport
- Area 8 — Taunton, Fall River
- Area 9 — Hyannis, New Bedford
- Area 10 — Plymouth
- Area 11 — North Shore
- Area 12 — Greater Boston (Sanders Theater)

The changes indicated above have accomplished a certain amount of decentralization, they have made it possible better to satisfy the desires of local chairmen especially regarding the time of meetings, and finally these changes have made it easier for doctors to get to the meetings. In general, the results have been very gratifying.

In the eleven teaching areas outside Boston, 36 exercises have been conducted under the auspices of this committee. With one or two exceptions, the attendance has been excellent, revealing a definite increase over previous years. However, as in previous years, actual attendance reports are not available. This past year has witnessed the development of a very satisfactory liaison between local chairmen and the Boston group. Undoubtedly this has contributed greatly to the success of the meetings.

Sanders Theater Course

This is the fourth year of these meetings. As usual, under the able leadership of Dr. Hurxthal and the various

program chairmen, an attractive program was arranged. This year it seemed inadvisable to send out registration cards so that we have no figures on total registration. Judged from average attendance, however, the meetings were as well received, if not better, than in previous years.

General Discussion

The aim of postgraduate medical instruction as conducted by the Massachusetts Medical Society is to make available to all physicians in the Commonwealth a certain amount of useful information without charge and with the express purpose of thereby improving medical care. There is no question concerning the interest of physicians in such an endeavor. The real question that constantly confronts your committee is how we can best accomplish the objectives of such an endeavor.

In the light of recent developments in the practice of medicine, it is our belief that this problem merits the attention of all thoughtful physicians. Anything we can do to close the gap that now exists between available medical knowledge in teaching centers and in outlying districts or to stimulate the formation of local teaching centers scattered throughout the State, or both, will help solve the problem of medical manpower distribution and will also help answer some of the current criticisms of medical practice.

Viewed in this larger sense, there is still plenty of work ahead for your committee. It is suggested that we devote more attention to community needs and explore the possibilities of closer affiliation with the Department of Public Health and with the various scientific bodies with headquarters hereabouts. It is also suggested that your committee endeavor to enlist the support of the deans of the medical schools with the thought in mind that it is perhaps not too much to suggest that the medical schools have a certain responsibility in this work.

Of course, a good deal of graduate teaching is going on outside the scope of your committee, and actually some areas have set up teaching courses conducted entirely by local talent. A notable example is the course conducted for the past three years by the Springfield group. Such endeavors should be encouraged, and possibly your committee could help in the formation of study groups in other areas.

These and other considerations are the concern of this committee. We are very conscious of the increasing importance of this work. It is our hope that with the continued co-operation of the members of this Society there will be a constant improvement in the type and scope of postgraduate medical instruction for the betterment of medical practice in this state.

W. R. OHLER, *Chairman*

APPENDIX NO. 21

COMMITTEE ON MEDICAL ECONOMICS

At the request of the Council, the Committee has reviewed the policies of the Society concerning activities that might be questioned by the federal Government in relation to anti-trust laws. Legal counsel assures us that so far as the Blue Shield is concerned the Society and Blue Shield are clear. We are advised that investigation of other activities of the Society is not necessary at this time.

ALLAN M. BUTLER
VLADO A. GETTING
HENRY A. ROBINSON
MERRILL C. SOSMAN
ELMER S. BAGNALL, *Chairman*

APPENDIX NO. 22

COMMITTEE TO MAKE RECOMMENDATIONS AS TO FUTURE DIRECTORS OF THE BLUE SHIELD

To hold office until 1952

Mr. Eban H. Ellison, Jr., reappointment
Mr. Joseph K. Milliken, Jr., reappointment

revert to the Building Fund. However, the true liquidating value of the Fund must be based on the market value, not book value, of the securities held and in the case of the General Fund, the market value of the securities is \$9183 less than their book value, so actually only \$19,401 can be added to the Building Fund out of surplus this year, and the difference in market and book values held as reserve.

At the beginning of 1948 the total assets of the Building Fund in cash and book value of securities stood at \$76,072. Adding to this the \$19,401 conveyed from the surplus in the General Fund and \$2127 income from the Building Fund securities brings the amount to \$97,600. But loss from sale of securities of \$768 and difference between the market and book values of the securities of \$2154 must be deducted to bring the actual cash value of the Building Fund to \$94,678 at the end of the year.

There is no particular reason to maintain a large General Fund. The amount derived in income from its securities is only 4 per cent of the Society's total income for general expenses, whereas 90 per cent of the income for this purpose comes from assured annual dues. But there is great merit in increasing the Building Fund in every possible way in anticipation of the time permanent headquarters are established and to assure their maintenance without being dependent on income from dues, which should be spent for general expenses covering the activities of the Society.

We enter 1949 with a grand total of assets in cash and securities of \$381,771, an increase of \$24,243 over the previous year.

During the year the following changes have been made in the portfolios. In the General Fund, \$20,000 U. S. Treasury 2½ per cent bonds due 1972/67 were sold, as were 60 shares Consumers Power 4½ preferred stock and 80 shares Monsanto Chemical Company common stock. Purchases in the General Fund included \$10,000 U. S. Treasury 2 per cent bonds due 1954/52, \$10,000 U. S. Treasury 2 per cent bonds due 1951/49, 100 shares Newmont Mining Corporation common stock, 300 shares Wisconsin Electric Power common, 25 shares Allied Chemical and Dye common, 125 shares General Electric common, 70 shares Firemans Fund Insurance and \$6000 Peoples Gas Light and Coke 3 per cent bonds due December, 1963. In the Building Fund were sold 30 shares Consumers Power Company 4½ per cent preferred stock and 50 shares Monsanto Chemical Company common, while purchases were made of 50 shares Newmont Mining Corporation common, 15 shares Abbott Laboratories common, 20 shares Gulf Oil Corporation, common and \$3000 Peoples Gas Light and Coke 3 per cent bonds due 1963.

Because of an added amount of work connected with the Federal Old Age and Unemployment taxation and the State unemployment taxation, retroactive for several years, the Assistant Treasurer made a welcome entry into active participation in the Treasurer's office to handle all tax correspondence. His services have been greatly appreciated, and his status, emerging from that of a figurehead, to one in which he has more intimate contact with the office, should bring with it mutual gratification.

Upon proper authorization the Treasurer wrote a detailed description of the Society's activities to the Treasury Department, Washington, D. C., to ascertain if any operations might be bringing us unwittingly nearer to the brink of liability for federal income taxation as a corporation. The reply was most reassuring, taking up item for item, to affirm that, as now conducted, our endeavors would not endanger our income-tax exemption.

Before it was finally voted to increase the dues to \$25 in 1948, the committee appointed to study the need reported that they advised this amount, somewhat above coverage for the expenses at that time, in order that the dues would not require further increase for many years to come. With this laudable aim in view it is important for the members to consider the narrow margin between the budget of \$142,000 for 1949 and the estimated income of

\$150,000. Whereas it is possible that the whole amount budgeted will not be spent, care should be taken in long-range contemplation to plan to confine the extent of the Society's activities within the limits of the stable income, if it should be deemed advisable that some lines of effort be expanded, others would by necessity have to be curtailed.

COMPARATIVE EXPENSES 1947 AND 1948

	1947	1948
Salaries		
Secretary	\$3 820 64	\$8 300 00
Executive Secretary	4 800 00	4 800 00
Treasurer	2 500 00	2 000 00
Assistant Treasurer	0 00	500 00
Director of Medical Information and Education	3 750 00	8 000 00
Expenses		
President	214 82	338 51
President Elect	74 04	4 95
Secretary	2 779 61	3 412 00
Treasurer	2 059 00	1 996 27
Director of Medical Information and Education	469 39	3 364 22
Delegates to A. M. A.	676 23	2 860 36
Cutting luncheons	450 00	290 00
Refunds to district societies	4 000 00	8 000 00
New England Council dues	100 00	100 00
Clerical work	5 162 00	6 145 00
General administrative	3 562 89	4 155 95
Shattuck Lecture	200 00	16 66
Donation to Boston Medical Library	1 180 00	26 675 00
Premium on pension plan	4 233 80	4 080 40
Committee Expenses		
Arrangements	0 00 (profit)	0 00
Ethics and Discipline	60 49	43 92
Executive	232 09	33 05
Fee Schedule	348 35	0 00
Finance	0 00	0 00
Industrial Health	17 80	41 87
Headquarters	7 421 19	4 166 20
Legislation	4 311 30	4 536 15
Medical Economics	63 34	0 00
Medical Defense	1 474 51	3 730 00
Membership	137 77	66 11
Postwar Loan Fund	151 12	0 00
Postwar Planning	0 62	0 00
Information Bureau	3 128 72	2 676 48
Postgraduate Education	3 097 14	4 499 50
Public Health	195 91	98 39
Public Relations	451 61	304 29
Publications	2 346 12	88 81
Rehabilitation	71 03	0 00
Special Services	361 28	0 00
To Study Malpractice Insurance	148 91	0 00
Tax-Supported Medical Care	0 00	36 31
Advisory School Medical Services	29 88	0 00
To Consider Secretary as full-time Officer	19 74	0 00
To Meet with Rehabilitation Centre	0 00	27 19
On Expert Testimony	0 00	88 83
National Emergency Service	0 00	213 55
On Council Rules	0 00	66 24
Miscellaneous		
Net loss on sales securities General Fund	0 00	1 026 14
To carry New England Journal of Medicine	0 00	5 000 00
Taxes		
Federal Unemployment	462 99	59 49
Federal Old Age	65 58	198 31
Massachusetts Unemployment	0 00	535 39
Prior Years Massachusetts Unemployment	0 00	2 364 90
	\$64 630 11	\$114 640 44

APPENDIX NO 29

AUDITING COMMITTEE

The Auditing Committee appointed the firm of Hartshorn and Walter, accountants and auditors, to audit the books and accounts of the Massachusetts Medical Society. This audit and account are hereby approved by us.

The analysis of the revenues and expenses of the Society and the balance sheet of the condition of the funds of the Society have been inspected and approved by us.

FRANK T. DOWNEY
HOWARD B. JACKSON, Chairman

Ethics and Medical Defense Act of the Society, and the Principles of Medical Ethics of the American Medical Association

The committee recommends that amended by-laws be checked for correctness of form by the assistant editor of the *New England Journal of Medicine*

ELMER S BAGNALL
ALBERT A HORNER
FRANK R OBER
EDWARD P BAGG, *Chairman*

APPENDIX NO 26

COMMITTEE ON DIABETES

The Committee has met and considered various means of extending plans for bringing under treatment the undiscovered cases of diabetes of the Commonwealth. The efforts already made by some district societies indicate clearly that the district societies can really carry out diabetes-detection programs most efficiently. The importance of this problem has been recognized by other committees of this society, and it is the desire of the Committee on Diabetes to present with the Committee on Public Health and the Committee on Industrial Medicine the following resolution

WHEREAS, the Massachusetts Medical Society has already approved an attempt to find the undiagnosed diabetic patients of the Commonwealth and bring them under treatment, and

WHEREAS, representatives of a large number of industries in the State have expressed a desire to co-operate with efforts directed at the discovery of latent diabetes in order to secure early treatment,

BE IT RESOLVED that the Council of the Massachusetts Medical Society recommend suitable action by the officers and committees of the district medical societies to carry out appropriate programs aimed at the discovery of diabetes in the community consistent with the Diabetes Detection Program and Diabetes Week sponsored by the American Diabetes Association

FRANK N ALLAN
GEORGE BALLANTINE
JOSEPH ROSENTHAL
JAMES L SMEAD
JAMES H TOWNSEND
PRISCILLA WHITE
HOWARD F ROOT, *Chairman*

APPENDIX NO 27

COMMITTEE ON VETERANS AFFAIRS

A meeting of this committee was held at 8 Fenway on March 9, 1949, to confer with Drs Pratt, Adler and Schultz, of the Veterans Administration, concerning their policies in the outpatient treatment of veterans with neuropsychiatric disabilities

After an extensive study of all neuropsychiatric patients under fee-basis treatment, it has been determined that in general their difficulties are of such complex nature as to require special psychiatric techniques. Unless they receive such specific care, their condition tends to become static, and the final outcome is usually a chronic illness refractory to further measures

In Metropolitan Boston, where specialist resources are readily available, patients are either accepted for treatment at the Mental Hygiene Clinic, Boston Regional Office, or are authorized fee-basis psychotherapy by certified specialists in neuropsychiatry. In exceptional cases or in such areas where specialists' care is not readily available, patients are authorized treatment by the family physician. As required by Veterans Administration regulations, treatment reports are reviewed monthly by a psychiatrist to determine the need for continuation of treatment or necessary changes

On the basis of a number of such reports, it has become obvious that clarification of certain clinical points is in order. The following recommendations are offered as a guide to family physicians treating veterans with neuropsychiatric disabilities

Overemphasis on treatment of functional somatic complaints affords only temporary symptomatic relief while focusing the patient's attention on areas that are actually remote from the real cause of his illness. This has the effect of supporting the patient's reluctance to approach his complaints in emotional terms

Reliance on sedatives or hypnotics to control emotional distress for long periods has led in a number of cases to drug habituation and has thereby created an additional serious problem

Liberal use should be made of either fee-basis psychiatrists or the Mental Hygiene Clinic of the Veterans Administration, Boston Regional Office, for psychiatric consultation, re-evaluation or other specific psychiatric care

Lastly, physicians are reminded that the *Veterans Administration regulations permit the authorization of treatment only for service-connected disabilities*. Patients are not entitled to reimbursement for the treatment of any other illness that may occur concomitantly with their adjudicated service-connected disabilities

The Committee urges that these recommendations be brought to the attention of members of the Society in the *New England Journal of Medicine*. The committee further recommends that all matters of difficulty between the Veterans Administration and the doctors, arising out of the care of veterans, shall be referred to the Board of Review of the Massachusetts Medical Society for their consideration

SAMUEL BACHRACH
JOHN M BARRY
KENNETH A BROWN
JOHN F COVIL
JAMES M FAULKNER
GEORGE S RETHOLDS
HARVEY A KELLY, *Chairman*

APPENDIX NO 28

REPORT OF THE TREASURER

With the increase in resident annual dues in 1948 from \$10 to \$25, income from such dues rose from \$59,020 in 1947 to \$134,960. Income from nonresident dues rose from \$2244 to \$2514. Income from censor fees of \$1335, in 1947, fell to \$1053, in 1948. Net profits from the Committee on Arrangements, \$6234 in 1947, fell to \$3153 in 1948, and that from the New England Postgraduate Assembly \$528 in 1947, rose to \$1146 in 1948

Among the endowment funds, the Phillips Fund is the only one with unrestricted use of income, and \$200 was derived from this source in 1948. The incomes from the restricted funds have been applied this year to reduce expenses according to their respective purposes, as will be seen in the detailed expense account—the Brickley Fund toward luncheon expenses of the Committee on Ethics and Discipline, the Shattuck Fund toward the stipend given the Shattuck lecturer, and the Cotting Fund toward the cost of the Cotting luncheons

Income from the securities in the General Fund rose from \$5895 in 1947 to \$6571 in 1948, and in the Building Fund from \$1906 to \$2127. In 1948 there was a loss on sale of securities in the General Fund of \$1026, and in the Building Fund of \$786. This was due to the sale of some of the holdings in Monsanto Chemical Company common stock and Consumers Power Company 4 5 preferred stock in both funds on advice of our investment counselors

The book value of securities held in the General Fund has risen from \$199,150 to \$218,907 and in the Building Fund from \$74,308 to \$75,347. The principal of the Endowment Funds remains at \$28,166

Total revenue in the General Fund was \$149,998 for 1948, and total expense was \$114,640, leaving a surplus of income over expenditures of \$35,358

By previous vote of the Council, the total assets of the General Fund are to be pegged at \$250,000, and any surplus for a given year to be diverted to the Building Fund. At the beginning of 1948 the assets of the General Fund, calculated on cash and book value of securities, was \$243,226, leaving presumably \$6774 to be added to bring the total to \$250,000 and the remainder of the surplus or \$28,584 to

This patient did not have hypertension. Blood dyscrasia was certainly not noticeable in the report.

Let us turn now to the differential diagnosis of the abdominal mass, and then let us see if there is any one diagnosis that will explain both these findings. An abdominal mass that appears to be freely movable, in a patient such as this, may be an ovarian cyst or tumor. I will not go into a classification of ovarian tumors here. A pedunculated fibroid could produce such a mass and so could a cyst of the mesentery, carcinoma of the bowel and, finally, the spleen. Spleens are occasionally on a very long pedicle and may be found anywhere in the abdomen.

Is there any diagnosis that would explain both the post-menopausal bleeding and the presence of a movable mass in the abdomen? Ovarian tumors or cysts that produce estrogen and in turn cause growth of the endometrium and bleeding from it should by definition produce endometrium. I am very much interested in the statement that the uterine curettings were not grossly abnormal. In a woman ten years past the menopause, who has received no estrogen therapy by mouth or parenterally, that statement should mean that there were no uterine curettings, and I should like to ask, if it is a fair question, whether there were curettings at all or whether this statement means that there were curettings but they were not grossly abnormal.

DR MARSHALL K. BARTLETT: There was a moderate amount of tissue that appeared as a result of curettage.

DR ULFELDER: The statement that the uterine curettings were not grossly abnormal means, then, that this did not look like a malignant lesion of the uterine fundus. Were the curettings similar to those ordinarily seen in the pre-menopausal woman?

DR BARTLETT: Essentially the same, I believe.

DR ULFELDER: That very definitely raises the possibility that this patient was making estrogen and therefore growing an endometrium. However, one can get from the post-menopausal uterus material that is reported later by the pathologist as showing atrophic endometrium. If one cures carefully, I am sure it is always possible to get a little something, although occasionally we see nothing at all.

A possible diagnosis therefore in this case is a tumor of the ovary, which made estrogen and caused secondary development of endometrium in this post-menopausal uterus. Such a tumor would be either a granulosa cell or a thecoma or, less likely, a papillary cystadenoma. Carcinoma of the uterus and polyp of the endometrium should have been detected in the curettings, probably grossly. If senile changes had been noted in the vaginal mucous membrane they would have been described in the protocol, particularly since that must have been in the operator's mind as a possible explanation

for the bleeding when he examined this patient. Fibroid could explain the mass but not the bleeding. Fibroids of the uterus do not produce bleeding in the post-menopausal woman.

The only diagnosis I can see that will explain both findings on the basis of one lesion is an estrogen-producing tumor of the ovary, with growth of the endometrium secondary to it. There is one other possible explanation for her bleeding, which I neglected to mention, and that is resumption of normal menstruation. You will note from the protocol that there was some rhythmicity to this woman's bleeding, and that the bleeding was somewhat like periods in that it took place for about five days and then ceased altogether until the next episode. I recall no case in which this has occurred as long as ten years after a cessation of periods on physiologic grounds. I think it is not uncommon for women to have a period or two, as long as eighteen to twenty months after the cessation of periods, but I think that is a most unlikely explanation for the bleeding in this woman after this long interval.

Endocrine-producing tumors of the ovary are rare, and one has to make, therefore, a rare diagnosis, to explain both these findings on the basis of one lesion. It is so rare that I think it is unlikely in this patient. I think it is more likely that these two findings were not associated. I think she had a mass, and I think she had post-menopausal bleeding. I think the post-menopausal bleeding probably will not be explained, and I think the mass was an entirely independent condition. I would consider a spleen as the most likely mass in this patient. The mass was rather high on the left side, and when it was displaced, it was displaced to the right but not down. I am also interested in the statement that the pelvic examination was not remarkable. I think I will "stick my neck out" and say that this patient had a wandering spleen, that she did not have any good explanation for post-menopausal bleeding, and that it is possible, but not likely, that she had an estrogen-producing tumor of the ovary.

DR TRACY B. MALLORY: Is there any further comment? Dr Bartlett, I wonder if you would tell us what you found at operation.

DR BARTLETT: This case was a good example to me of the value of re-examining the abdomen under anesthesia, because this woman had a really sizable mass, — I think "grapefruit size" is a fair description of it, — and yet we had all completely missed it. The mass was easily felt under anesthesia, and it seemed to be symmetrical and smooth. Although when first felt it was in the left side of the abdomen it could very easily be rolled across into the right side, off into the right gutter, so to speak, and then back again. It seemed to lie a little more easily on the left than on the right, and on bimanual examination we were not able to make out any connection with the uterus. We could move the abdominal mass, so far as we could tell, without

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35291

PRESENTATION OF CASE

A fifty-eight-year-old Italian, para IV widow entered the hospital because of vaginal bleeding.

Ten years before admission the patient passed through a relatively uneventful menopause and had no further bleeding until six months before entry, when she suddenly began to spot. This spotting lasted five days and then disappeared completely. She had a similar episode of bleeding two months before admission, which also lasted five days, and then a third episode a month later. There was no associated vaginal discharge or pain and no other symptoms. There was no history of estrogen medication.

Her catamenia had begun at twelve years of age, and her menstrual periods were always regular. She had had a gall-bladder operation fifteen years previously and a second abdominal operation, for some unknown reason, a few years later.

Physical examination showed a markedly obese woman. Examination of the heart and lungs was negative. The abdomen was so obese that no masses could be made out. There was a scar in the right upper quadrant.

The blood pressure was 135 systolic, 85 diastolic. The temperature, pulse and respirations were normal.

Examination of the urine was negative. The blood showed a hemoglobin of 13 gm and a white-cell count of 6500, with 63 per cent neutrophils. A vaginal examination was not remarkable.

An operation was performed on the second hospital day. Under anesthesia, a grapefruit-sized abdominal mass was palpated, on the left side above the pelvic brim, but could be pushed across the midline to the right side. The uterine curettings were not grossly abnormal.

A laparotomy was then performed.

DIFFERENTIAL DIAGNOSIS

DR HOWARD ULFELDER The history is that of an obese woman who had her menopause ten years before, who was essentially well in all other respects, who had recurrent episodes of vaginal bloody spotting for six months prior to operation and who, under anesthesia, proved to have a movable mass the size of a grapefruit.

I think it might be useful in this particular case to single out the two outstanding findings and run over the differential diagnosis of each one. The first one, of course, is post-menopausal vaginal bleeding. A common cause for this—in fact, the most common cause nowadays—is exposure to the action of estrogens. We are told that this patient was not given estrogen medication, we must not overlook the fact that she may have been producing her own estrogen. There are ovarian tumors that make estrogen in large quantities. These are the granulosa cell tumor and the thecoma. Certain other ovarian tumors also produce small quantities of estrogen—even papillary cystadenocarcinoma of the ovary occasionally has associated endometrial bleeding without a malignant lesion of the endometrium.

A second cause for post-menopausal vaginal bleeding is a tumor of the uterus. This may be either malignant—carcinoma of the uterine fundus or of the cervix—or benign—a uterine polyp. There are a number of other causes of post-menopausal bleeding. A common one is the senile change frequently noted in the vagina. Senile vaginitis is frequently associated with bloody spotting. It is usually also associated with some degree of vaginal discharge and local irritation. Some people believe that there are senile changes in the endometrium corresponding to this visible change in the vaginal mucous membrane, and it has occasionally been postulated that bleeding from a senile endometrium or endometritis can occur just as we see bleeding from senile vaginitis. This has never been proved. Occasionally, in hypertension, we find post-menopausal vaginal bleeding explained on no other basis. This has been described as uterine apoplexy. It is a concept that is not very strongly held by anyone today but is occasionally mentioned and should be included in the differential diagnosis of this condition.

Blood dyscrasias, of course, can produce bleeding from the uterus as from any other part of the body, and they must be considered. And, finally, there is a group of patients in whom no explanation is ever found for the post-menopausal vaginal bleeding. Unfortunately this is a rather large group. The present state of our knowledge about this symptom is such that there are many patients in whom the most thorough study fails to reveal any cause for post-menopausal bleeding.

Some diagnoses that I have mentioned may be excluded on the basis of the protocol.

of gas was seen in the descending colon and rectum.

The patient was given fluids and blood intravenously and improved somewhat. The hemoglobin, hematocrit and total protein dropped from 17.5 gm per 100 cc, 51 per cent and 7.8 gm respectively, to 15.5 gm per 100 cc, 46 per cent and 6.5 gm. The blood pressure reached a maximum of 110 systolic, 60 diastolic. A urine specimen obtained on the second day gave a ++ test for albumin, and the sediment contained many granular and hyaline casts and 15 to 20 red cells and 10 to 20 white cells per high-power field. The nonprotein nitrogen was 82 mg per 100 cc. The patient's condition never improved enough to warrant operation, and from the middle of the second hospital day, in spite of large amounts of intravenous fluids and blood, she became increasingly comatose, the blood pressure dropped, and the pulse became more rapid and weak. Drainage from a stomach tube at first was dark brown but later became blood stained, and no peristalsis was ever heard. The total urinary output during the patient's hospital stay did not exceed 400 cc. She died early on the third hospital day.

DIFFERENTIAL DIAGNOSIS

DR JOHN B. MCKITTRICK: There is only one diagnosis that I can make from the history as recorded, that is, intestinal obstruction, with perforation and peritonitis. Whether one could be more specific than that is problematic, since we have little information beyond the salient features of the short, acute illness. Whether the acute episode was of ten days' or three days' duration is not quite clear in my mind. The history described a "cold and pain in her back, for which she went to bed" ten days before admission. Apparently during the intervening seven days until she began to have lower abdominal crampy pain, and following that vomiting, the course was not remarkable. One does not know whether the back pain persisted and later merged with the lower abdominal cramps, whether there was a subsidence of the back pain and apparent recovery from the cold, or whether symptoms persisted during this period and merged into the more acute and dramatic picture developing three days before admission.

The past history reveals only that twelve years previously a Mikulicz procedure was done for infarction of a segment of sigmoid. It is to be presumed, then, that in the intervening period the patient was free of consequential complaints.

The physical examination and chemical picture on admission to the hospital give us little help beyond confirming the clinical impression of intestinal obstruction. A dehydrated patient in shock, semicomatose, with distended abdomen and evidence of hemoconcentration, is in perfect accord with the picture one sees in late intestinal obstruction. No mention is made of abdominal tenderness, and I think wisely because a patient in this condition

loses the normal response to abdominal palpation. The subsequent course of the blood picture, with return to more normal levels following hydration, electrolyte replacement and transfusion, emphasizes this aspect of the obstruction problem. Such replacement therapy is essential to proper management but must be followed by correction of the underlying disease. In this patient the process was so advanced that operation was not deemed practical.

The elevated nonprotein nitrogen, oliguria and urinary findings of hyaline and granular casts and a few red and white cells do not, I believe, indicate renal disease. Such findings are perfectly consistent with dehydration associated with intestinal obstruction.

Can one, from the information given, reconstruct the course of events and localize the lesion? To go back ten days before admission we find that she complained of what she called a cold and pain in her back. Pain in the back in intestinal obstruction is an interesting symptom, and while not common, when present is very suggestive of strangulation obstruction. However, it is inconceivable to me that this patient had strangulation obstruction for a period of ten days. Therefore I am forced to exclude the symptom of pain in the back from the episode immediately preceding admission. We are then left with a three-day story beginning with lower abdominal crampy pain and, somewhat later vomiting. This suggests that the obstruction was low, rather than high, since the vomiting was a delayed symptom. Vomiting is a much more prominent feature in small-bowel than in large-bowel obstruction. On the other hand, one is more apt to find lower abdominal cramps in large-bowel than in small-bowel obstruction. About 20 per cent of patients, however, will localize pain in small-bowel obstruction below the umbilicus, so that one cannot depend upon the localization of pain entirely. The chemical changes with the rather severe dehydration suggest a marked degree of vomiting within a relatively short period of three days. This is much more suggestive of small-bowel obstruction. It would be unusual, I think, for a patient with the ordinary type of large-bowel obstruction to vomit enough to cause this degree of hemoconcentration and chemical imbalance in this space of time. The x-ray films of the abdomen should help us, and from the description, I would be more inclined to call this large bowel rather than small bowel. Usually, when one has a single loop of small bowel as much dilated as this, the remaining small-bowel pattern is apt to be proportionately distended. On the other hand, one may get tremendous distention of large bowel with relatively little distention of small bowel, or for all practical purposes no distention of small bowel if the ileocecal valve is competent. In a case of an isolated loop of small bowel, however, such as one might find in strangulation

moving the uterus, but one must not forget that this was a very obese patient. This examination under ether gave us the information on which to decide to do a laparotomy, and when that was done it was apparent that the mass was a cyst arising in the left ovary on a long, stretched-out pedicle. It was of the size described and was smooth on the outside, with a moderately thick wall but with no external projections on it. The tubes and the other ovary were not unusual. The uterus was somewhat larger than one would expect after the menopause but again was not definitely beyond normal limits. A total hysterectomy was carried out, both tubes and ovaries being removed.

CLINICAL DIAGNOSIS

Ovarian cyst

DR ULFELDER'S DIAGNOSES

Post-menopausal uterine bleeding of unknown etiology
Wandering spleen
Second choice: estrogen-producing tumor of ovary

ANATOMICAL DIAGNOSIS

Granulosa cell tumor of ovary

PATHOLOGICAL DISCUSSION

DR MALLORY: The specimen Dr Bartlett removed was a soft, fluctuant tumor mass, which looked and felt like a cyst. On cutting across it, we found that there were cystic areas and also solid tumor foci. One of the cystic areas contained some almost cheesy material. There were also shaggy, papillary masses projecting into the cyst. From the gross examination we thought that it was probably a papillary cystadenoma of the ovary, and were considerably surprised when the microscopical sections came through to find that the solid portions of the tumor showed a very characteristic, unmistakable pattern of granulosa cell tumor. The endometrium was not obviously hyperplastic. There was slight cystic dilatation of some of the glands, but the epithelium was fairly tall, and was not of the atrophic type seen in the senile cystic endometrium. There was a very mild hyperplasia present.

Are there any questions that anyone would care to ask?

DR ALFRED KRANES: I still do not understand why Dr Ulfelder started what sounded like a perfectly logical diagnosis, but because of its rarity, made a rarer diagnosis.

DR ULFELDER: In my experience a wandering spleen is less rare than granulosa cell tumor.

DR KRANES: Really?

DR MALLORY: I will certainly back up Dr Ulfelder in his statement that when uterine cancer is excluded we are unable to find any pathological reason for post-menopausal bleeding in the majority

of cases when we are supplied with the ovaries and uterus.

DR BARTLETT: Dr Mallory, would this endometrium be unusual, in a case of unexplained post-menopausal bleeding?

DR MALLORY: I do not believe there was enough change in it so that I would have probably picked it up, if I had been given the curettings alone. I do not believe I would have made a diagnosis of hyperplasia, and I would not have suspected at all strongly granulosa cell tumor. Sometimes, when there is frank hyperplasia, we have been able to suggest the diagnosis on the basis of curettage.

CASE 35292

PRESENTATION OF CASE

A forty-nine-year-old housewife entered the hospital because of abdominal pain and vomiting.

Ten days before admission she had a cold and pain in her back, for which she went to bed. Three days before admission she noted the onset of lower abdominal crampy pain and somewhat later vomiting. She failed to pass anything by rectum except under the stimulus of enemas, when on two separate occasions small amounts of gas and hard feces were obtained. The vomiting continued and became brown in color. On the day of admission she became cold and clammy, and the pain diminished.

Twelve years before admission a Mikulicz procedure had been performed, with resection of an infarcted segment of sigmoid. One month later a laparotomy was performed, and obstructed loops of small bowel were freed from around the sigmoidostomy. One year later the sigmoidostomy was closed.

Physical examination revealed a semicomatose, very pale, clammy, cold woman in no acute pain. The lips were dry, the chest was clear, and the abdomen was distended and doughy with a nontender hernia (3 cm in diameter) in the left upper rectus scar. The skin over the hernia showed a slight, bluish discoloration and was hot to the touch. No organs or masses were palpable, and no peristalsis was audible. Pelvic examination showed a lacerated, freely movable cervix, no masses or tenderness was made out. Rectal examination was likewise negative for masses and tenderness, the rectum was empty.

The temperature was 103.2°F, the pulse 100 and the respirations 25. The blood pressure was unobtainable.

Examination of the blood revealed a red-cell count of 5,000,000, with a hemoglobin of 16 gm, and a white-cell count of 16,000. An x-ray film of the chest was normal. A plain film of the abdomen showed a loop of bowel measuring 12 cm lying across the right midabdomen, and numerous moderately dilated loops of small bowel. A small amount

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CORNERSTONE OF THE TEMPLE

ISRAEL'S Hebrew University-Hadassah Medical School, in accordance with an announcement previously published, was inaugurated on May 17 in a joint international ceremony taking place simultaneously in Jerusalem and at the Israeli Consulate in New York. Participating in the creation of the first school of medicine in the new state were Dr Chaim Weizmann, president of Israel, and American medical scientists, teachers and administrators

A symbolic part of the ceremony was the presentation by Warren R. Austin, United States ambassador to the United Nations, of a block of Vermont marble. This stone, a product of the same quarry that is supplying material for the United Nations permanent headquarters, was ac-

cepted by Mrs Haim Yassky, of Jerusalem, widow of the late Hadassah medical director. It will become 'cornerstone of the cornerstone' of the new medical-school building soon to be erected on Mt Scopus, near Jerusalem

From the days of ancient Israel and the lessons in hygiene that came from Judea, Jewish medicine has traced its brilliant course. As Dr Weizmann said, the school will be another "vehicle in the struggle to make the ideals of social progress and democracy realities, not only in Israel but throughout the Middle East"

It is another aspect of America's program to make the benefits of scientific advances available to other governments and other peoples. It is another instance of American generosity, and a manifestation of American Jewry's profound awareness of the meaning of Jewish history and tradition and their sensitivity to the cultural and physical needs of Israel today

May the building of this university on a hill in Palestine be another step in the bringing of peace to a troubled land, and to a scattered race a home that it may look to, even if only a few inhabit it!

"BY THEIR FRUITS"

AFTER the death in September, 1947, of Dr Robert Nason Nye, late editor of *The New England Journal of Medicine*, certain sums of money donated by his friends to the American Cancer Society were set aside for a definite purpose. This particular purpose, as announced in the editorial columns of the *Journal* on February 26, 1948, was an evaluation of the effects of radiation on the personnel of x-ray departments

Approximately \$2500 had been donated, which was later augmented by another \$1000 from an anonymous giver, and this sum was voted as a grant to the Massachusetts General Hospital for the study in question. Already this study has borne first fruits, which are incorporated in the report by Hunter, Merrill, Trump and Robbins, appearing as the leading article in the present issue of the *Journal*

The technical terms in which much of this preliminary report is necessarily written suggest certain more easily comprehended conclusions. Scattered diagnostic radiation, formerly thought to be soft and

obstruction, it would be very easy to have an x-ray picture not dissimilar to that described. The small amount of gas seen in the descending colon and rectum may have passed the point of obstruction or may have been introduced at the time of the numerous enemas, so I think we must exclude this as a significant finding, particularly in view of the patient's condition.

It seems to me that the most logical explanation for this picture is an isolated loop of small bowel with strangulation of the mesentery causing infarction with subsequent perforation and peritonitis. I cannot fit the whole picture logically with the diagnosis of large-bowel obstruction. I say this because of the short history, the amount of vomiting, the degree of dehydration and the rapidity of the downhill course, all of which are much more consistent with obstruction of the small as opposed to the large bowel. The blueness described in the area of the hernia may well have represented the bloody fluid associated with strangulation obstruction, or could simply have been the peripheral collapse and local congestion associated with peritonitis. However, I would not be a bit surprised to find that the patient had purulent, bloody fluid within the abdominal cavity.

My diagnosis, then, is small-intestine obstruction, mechanical in nature, with strangulation, perforation and peritonitis. I can only guess at the mechanism. A loop of bowel could have been caught in the hernia, even though the hernia was soft, or an intra-abdominal band may have precipitated the difficulty.

CLINICAL DIAGNOSES

Strangulation obstruction of small bowel due to adhesions and volvulus
Peritonitis
Cerebral thrombosis

DR. MCKITTRICK'S DIAGNOSIS

Intestinal obstruction, mechanical, with strangulation, perforation and peritonitis

ANATOMICAL DIAGNOSES

Thrombosis of portal vein and branches of superior mesenteric vein

Infarction of segments and of small bowel

PATHOLOGICAL DISCUSSION

DR. AUSTIN L. VICKERY: The peritoneal cavity contained 700 cc of hemorrhagic fluid. Loops of both small and large bowel were distended, but although there were numerous old fibrous adhesions binding loops of jejunum and sigmoid to the old abdominal scars, there was no evidence of kinking of the bowel or signs of mechanical obstruction. Three segments of small bowel extending from mid jejunum to midileum were dark, reddish black and contained masses of blood in their lumens. The intestinal wall in these sites was edematous, friable and markedly hemorrhagic, with the intervening segments of small intestine presenting a bluish discoloration but lacking the picture of frank infarction of the previously mentioned loops. The mesenteric veins draining the infarcted sites of jejunum and ileum contained thrombi, which on microscopical examination proved to show signs of early organization. The portal vein showed a similar thrombotic process.

In the absence of an intra-abdominal inflammatory lesion, neoplasm or evidence of mechanical bowel obstruction, it appears that this case would fall into the category of idiopathic mesenteric venous thrombosis. In such cases the thrombi are bland in nature without evidence of inflammatory reaction in the wall of the vein or in the perivascular zones, and the etiology is obscure or conjectural. It is possible that a partial volvulus with torsion of the mesentery initiated the thrombotic process and that the resultant distention of involved intestinal loops effected a spontaneous reduction in the mechanical deformity.

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CORNERSTONE OF THE TEMPLE

ISRAEL'S Hebrew University-Hadassah Medical School, in accordance with an announcement previously published, was inaugurated on May 17 in a joint international ceremony taking place simultaneously in Jerusalem and at the Israeli Consulate in New York. Participating in the creation of the first school of medicine in the new state were Dr Chaim Weizmann, president of Israel, and American medical scientists, teachers and administrators.

A symbolic part of the ceremony was the presentation by Warren R. Austin, United States ambassador to the United Nations, of a block of Vermont marble. This stone, a product of the same quarry that is supplying material for the United Nations permanent headquarters, was ac-

cepted by Mrs Haim Yassky, of Jerusalem, widow of the late Hadassah medical director. It will become "cornerstone of the cornerstone" of the new medical-school building soon to be erected on Mt Scopus, near Jerusalem.

From the days of ancient Israel and the lessons in hygiene that came from Judea, Jewish medicine has traced its brilliant course. As Dr Weizmann said, the school will be another "vehicle in the struggle to make the ideals of social progress and democracy realities, not only in Israel but throughout the Middle East."

It is another aspect of America's program to make the benefits of scientific advances available to other governments and other peoples. It is another instance of American generosity, and a manifestation of American Jewry's profound awareness of the meaning of Jewish history and tradition and their sensitivity to the cultural and physical needs of Israel today.

May the building of this university on a hill in Palestine be another step in the bringing of peace to a troubled land, and to a scattered race a home that it may look to, even if only a few inhabit it!

"BY THEIR FRUITS"

AFTER the death in September, 1947, of Dr Robert Nason Nye, late editor of *The New England Journal of Medicine*, certain sums of money donated by his friends to the American Cancer Society were set aside for a definite purpose. This particular purpose, as announced in the editorial columns of the *Journal* on February 26, 1948, was an evaluation of the effects of radiation on the personnel of x-ray departments.

Approximately \$2500 had been donated, which was later augmented by another \$1000 from an anonymous giver, and this sum was voted as a grant to the Massachusetts General Hospital for the study in question. Already this study has borne first fruits, which are incorporated in the report by Hunter, Merrill, Trump and Robbins, appearing as the leading article in the present issue of the *Journal*.

The technical terms in which much of this preliminary report is necessarily written suggest certain more easily comprehended conclusions. Scattered diagnostic radiation, formerly thought to be soft and

comparatively harmless, is now shown to be relatively hard and penetrating. Consequently the roentgenologist must plan the protection of himself and his associates, so far as possible, from these marrow-reaching rays. The danger to the chance observer or to the patient is negligible. It is the daily exposure, month after month and year after year, from which the worker must be guarded.

Fortunately protection against scattered radiation is simple to attain by the means that are suggested, and the advice is offered that manufacturers of equipment could themselves provide more adequate protection for the examiner than is at present afforded.

DISTINGUISHED ALUMNUS

HARVARD University has again hewn to the line in its recognition of academic merit by the

whom twenty-five generations of medical students have held in affectionate regard, thus becomes the first Negro to hold a professorship in Harvard University.

Dr. Hinton, who was born in Chicago in 1883, graduated from Harvard College in 1905 and from Harvard Medical School in 1912, and then served as a voluntary assistant in the Pathological Laboratory of the Massachusetts General Hospital until 1915. He joined the staff of the Harvard Medical School in 1923 and has remained on it consistently ever since, his most recent appointment prior to his present professorship having been that of lecturer on bacteriology and immunology. He has been a fellow of the Massachusetts Medical Society since 1913.

In addition Dr. Hinton has been director of the Laboratory Department of the Boston Dispensary and chief of the Wassermann Laboratory of the Massachusetts Department of Public Health since 1915, and for the past thirteen years chief of the laboratories of the Boston Floating Hospital. He is a special consultant to the United States Public Health Service, consultant to the Massachusetts School for Crippled Children, and a lecturer at Simmons College.

Dr. Hinton, also an authority on rabies, is best known for his research in syphilology and for the development of the Hinton and the Davies-Hinton tests for syphilis.

Certain lines that were written in commemoration of the University's two-hundredth anniversary, a hundred and thirteen years ago, seem to reaffirm a still unaltered code:

*With freedom to think and with patience to bear,
And for right ever bravely to live*



WILLIAM A. HINTON, S.B., M.D.

appointment of Dr. William A. Hinton as clinical professor of bacteriology and immunology in the Harvard Medical School. Dr. Hinton, the friend

The Dental Recorder of July 1st, gives an account of curing tooth-ache by steam, on the Ohio River. The fellow who performed, had rights to sell, and of course belonged either to Connecticut or Massachusetts. People are injuring themselves exceedingly by drinking soda immoderately, this warm weather. They should abstain, too, from gormandizing on ice creams late in the evening.

Boston M & S J, July 18, 1849

MASSACHUSETTS MEDICAL SOCIETY



OPPORTUNITIES FOR PHYSICIANS

West Pembroke, Maine, offers a good opportunity for a general practitioner. There is no other doctor in the town than the retiring incumbent, Dr C E Chapman. The nearest hospital is in Eastport, twelve miles away. Any interested physician should make contact with Dr Chapman.

The Western Maine Sanatorium, West Minot, Maine, is in need of a physician. Application for further information should be made to Dr Lester Adams, superintendent.

DEATHS

DONOVAN — Arthur B. Donovan, M.D., of Brookline, died on June 22. He was in his fifty-second year.

Dr Donovan received his degree from Tufts College Medical School in 1923. He was a former member of the staffs of Mt. Auburn, St. Margaret's, Boston Living-in, Boston City, Harley and Whidden Memorial hospitals, and for the last five years had been chief surgeon of the Lumberman's Mutual Casualty Company. He was a member of the Boston Gastro-Enterological Society.

His widow, three sons and a daughter survive.

PERKINS — Franklin A. Perkins, M.D., of Dorchester, died on June 5. He was in his sixty-sixth year.

Dr Perkins received his degree from College of Physicians and Surgeons, Boston, in 1911.

His widow and a sister survive.

ROCKWELL — Alfred E. P. Rockwell, M.D., of Shrewsbury, died on June 19. He was in his eightieth year.

Dr Rockwell received his degree from Boston University School of Medicine in 1899. He was a fellow of the American Medical Association.

His widow and a brother survive.

ROSENBLUM — Carl W. Rosenbloom, of Holioke, died on March 2. He was in his sixty-third year.

Dr Rosenbloom received his degree from Tufts College Medical School in 1909.

His widow, a son, a daughter and three sisters survive.

TAURO — Emily C. Tauro, M.D., of Stoneham, died on June 23. She was in her forty-eighth year.

Dr Tauro received her degree from Boston University School of Medicine in 1927.

Her husband and a daughter survive.

MISCELLANY

UNIVERSITY OF VERMONT

A cardiovascular unit has been established at the Bishop DeGoesbriand Hospital by the College of Medicine of the University of Vermont for the special study and care of cardiovascular patients by means of modern scientific methods. It went into operation on July 1.

Investigative work, now in progress, is partly supported by funds from the National Heart Institute and the American Heart Association.

The staff of the unit is composed of W. Raab, M.D., F.A.C.P., Director, E. Lepeschkin, M.D., J. H. Bland, M.D., and R. J. Humphreys, M.D.

A cardiovascular outpatient clinic, conducted by C. M. Terrien, M.D., will function in close co-operation with the unit.

One of the first activities of the new unit was a refresher course in cardiovascular disease for practicing physicians, given in June. Guest speakers were Dr. Paul D. White, of Boston and Dr. Mercier Fauteux, of Montreal.

INTERNSHIPS IN VETERANS
ADMINISTRATION HOSPITALS

The Veterans Administration is offering 259 internships to qualified graduates of recognized medical schools in three hospitals beginning July 1, 1950. Pilot programs have already begun in two of these hospitals, at McKinney, Texas, and Chamblee, Georgia, affiliated, respectively, with Southern Medical College and Emory University.

The intern program will be conducted under the direction of the deans' committees and in co-operation with medical schools in the vicinity of the hospitals selected. Medical, surgical and rotating services are being offered.

AMERICAN NEUROLOGICAL ASSOCIATION

At the seventy-fourth annual meeting of the American Neurological Association, held in Atlantic City, New Jersey, from June 13 to 15, the following officers were elected for the year 1949-1950: president, Dr. Henry W. Woltman, first vice-president, Dr. Johannes M. Nielsen, second vice-president, Dr. E. Jefferson Browder, secretary-treasurer, Dr. H. Houston Merritt, and assistant secretary, Dr. Charles Rupp.

CORRESPONDENCE

HEPATITIS WITHOUT JAUNDICE

To the Editor: Dr. T. J. Domenici, in the January 20 issue of the *Journal*, reported the cases of 4 patients and stated that they had hepatitis without jaundice or hepatomegaly. That such a syndrome exists is not denied by any physician, but I should like to point out certain facts. If these patients had infectious hepatitis, the group formed a minor epidemic of the disease. It is curious that none of them or their associate nurses are said to have had jaundice, clinically or chemically.

A transient elevation in the cephalin-cholesterol flocculation and thymol turbidity tests is not, in itself, evidence of parenchymal liver damage. These laboratory phenomena indicate only that there is some nonspecific change in the serum proteins.

A more sensitive test of liver function — the bromsulphalein reaction — should be abnormal before it should be concluded that these patients had liver disease.

Visualization of the size of the liver by a scout film of the abdomen would have helped.

Of particular interest was the fact that the third patient had a diarrhea, consisting of four or five watery stools a day. In contrast to the battery of blood studies that she received, examination of her feces might certainly have been done.

It is not impossible that these patients had *amebic* hepatitis, or *amebiasis* without hepatitis, it seems to me.

I believe that the author is only entitled to assert, on the basis of his clinical reports, that he saw 4 young women with indeterminate gastrointestinal complaints and weight loss, who exhibited right-upper-quadrant tenderness and changes in certain laboratory tests that are usually considered evidence of liver damage. The evidence for infectious hepatitis is wanting.

Brooklyn, New York

JOHN W. WALSH, M.D.

Dr. Walsh's letter was referred to Dr. Domenici, who replied as follows:

To the Editor: The absence of jaundice, both chemically and clinically, in hepatitis cannot be considered unusual, since it was not uncommon in soldiers in World War II. Barker, Capps and Allen, in their article "Acute Hepatitis in the Mediterranean theater, including Acute Hepatitis without Jaundice" (*JAMA* 128:997-1003, 1945), state

that "hepatitis without jaundice was probably as common as hepatitis with jaundice in the Mediterranean theater"

The elevation of the cephalin-cholesterol flocculation and thymol turbidity was more than transient. The cephalin-cholesterol flocculation actually followed the clinical course rather closely. It is well known that these phenomena result from a change in serum protein. In some cases, this change is secondary to parenchymatous liver damage. Yardumian and Weisband, in their article "Cephalin-Cholesterol Flocculation Test in Liver Disease" (*Am J Clin Path* 13 383-392, 1943), state that "when there is parenchymatous liver damage the cephalin-cholesterol flocculation test is invariably positive." In their series of cases, all cases with liver disease gave a positive result, 90 per cent of unselected controls were negative. Rosenberg and Soskin, in their article "Comparison of Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function (with note on significance of hyperexcretion of hippuric acid)" (*Am J Digest Dis* 8 421-432, 1941), found "the cephalin-cholesterol flocculation test to be positive in 98 out of 100 cases of 'unquestionable' liver disease." In the same series of cases the bromsulphalein test was positive in only 68 per cent. It is the belief of the authors that the cephalin-cholesterol flocculation is the most sensitive test available.

As already indicated, it is not a unanimous opinion that the bromsulphalein reaction is the most sensitive test of liver function. As a matter of fact, some consider it one of the least sensitive tests. Moreover, it is accepted teaching that in determining liver damage, it is necessary to use a battery of tests since any one procedure may not be informative and actually misleading.

X-ray study was performed in all these patients, and no mention was made of liver shadow, although, admittedly, it was not looked for specifically.

Only 1 patient had diarrhea. This, however, does not excuse the lack of stool examination for ova and parasites. Amebic hepatitis or amebiasis without hepatitis, however, must certainly be an outside possibility in nurses who have not been out of New England or in the armed forces.

It is true that the gastrointestinal complaints were vague, but anorexia and sharply localized tenderness in the upper right quadrant were definite.

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Baldwinsville, Massachusetts

"TO LIMP"

To the Editor: In the review of *Peripheral Vascular Diseases: Diagnosis and treatment*, by David W. Kramer, M D, published in the *Journal* for June 30, the reviewer, obviously a competent person, makes the common mistake of interpreting the term "claudication" as "cramps." It is a small point, perhaps, but claudication comes from the verb "to limp," not "to close." It therefore means correctly "limp." When put as a question, incidentally, the correct answer has never been given me by student, house staff or visiting physician.

It is interesting that neither author nor reviewer has checked the correct definition of the word. Originally the description was an objective one, and not a subjective one of "cramps."

ALBERT S. MURPHY, M D
Boston, Massachusetts

Note: Neither Webster nor Dorland gives any other definition for claudication than limping or lameness, as indicated by Dr. Murphy.—Ed

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(Notices concluded on page xiii)

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Number 4

FRACTURES OF THE TIBIAL SPINES*

CHARLES H. BRADFORD, M.D.,† RONALD W. ADAMS, M.D.‡ AND H. KELVIN MAGILL, M.D.§

BOSTON

FRACTURES of the tibial spines, like all the less common fractures, receive so little attention in medical literature that even the specialists lose contact with the trends of treatment. It seems justified, therefore, to give this topic a thorough airing on the principle of "let sleeping dogs wake," even though our discussion may fail to contribute any vitally new ideas. The occurrence, recently, of 5 cases in our combined observation gives practical significance to such a review.

In this age of radiology it is apt to be forgotten that the entire foundation of knowledge of fracture pathology was established, before roentgenography, by keen observers in the nineteenth century who reconstructed the mechanics of the injury from their findings at autopsy. A search of the literature reveals that descriptions of tibial-spine fractures originated in just such a manner. According to Roth,¹ the first report came from Paris, the source of so much medical knowledge. There, in 1875, Poncet² described the case of a victim who had fallen three stories to his death. Examination of his knee showed "a tearing off of the spine of the tibia by the anterior crucial ligament, all the portion of bone that constitutes this eminence was torn off." In the place of the spine of the tibia, there was a hole that looked as if it had been made with a punch. Within a year, confirmation of a similar finding came from Germany. This patient received an injury to his knee when he was thrown out of a public house. The resulting hemarthrosis became infected, and amputation was performed, ending in the patient's death. On dissecting the knee joint, Dittel³ discovered that "the anterior crucial ligament was detached at its lower end, having torn with it an oval piece of the upper surface of the tibia."

These two simple descriptions contain almost all that need be known about the bone defect in this type of case. It is significant to note that this fracture is an avulsion, not so much of the *spine* of

the tibia, to which the anterior crucial ligament does not actually attach, as of the osteochondral fragment just anterior to the spine, where the cruciate ligament does insert. More properly then, these are "crucial-ligament fractures," as Lange⁴ calls them. They occur most commonly in the young or adolescent, and thus are counterparts of crucial-ligament tears in older age groups. The bony fragment may be torn off completely. More commonly

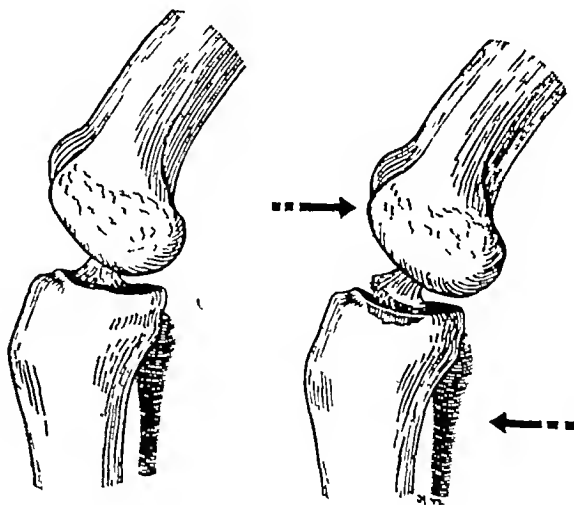


FIGURE 1 Mechanism of Fracture

it is only slightly displaced at its posterior margin beneath the spine of the tibia, whereas in the anterior portion it is elevated upward and backward as though it had stopped in the middle of a somersault (Fig. 1).

MECHANICS OF FRACTURE

The mechanism producing this displacement can easily be explained if one recalls that the anterior crucial ligament fastens the tibia to the femur much as a set of handcuffs fastens together the constable and his prisoner. It resists backward displacement of the femur on the tibia, or vice versa, and it also

*From the Sixth Surgical Service, Boston City Hospital.
†Instructor in orthopedics, Tufts College Medical School; assistant visiting surgeon, Boston City Hospital.
‡Assistant visiting surgeon, Orthopedic Service, Boston City Hospital; associate surgeon, Newton-Wellesley Hospital.
§Orthopedic surgeon, Out Patient Staff, Boston City Hospital.

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the knee. Since the cruciate ligament resists excessive motion of this type, it is natural that an undue strain in the rotational direction should cause the fracture. Pringle, as cited by Jones and Smith⁶ emphasized the importance of this mechanism and was able to demonstrate it experimentally on a specimen. We believe this to have been the mechanism in a case reported below (Case 4).

a typical case of this sort, in which the upper fragment of an old fractured spine had become embedded against the inner surface of the lateral condyle of the femur.

DIAGNOSIS

The diagnosis of fracture of an anterior cruciate ligament is suggested by a characteristic history



C



D

FIGURE 2 Roentgerograms of A. C.

Knees after reduction by manipulation, showing replacement of the anterior cruciate ligament.

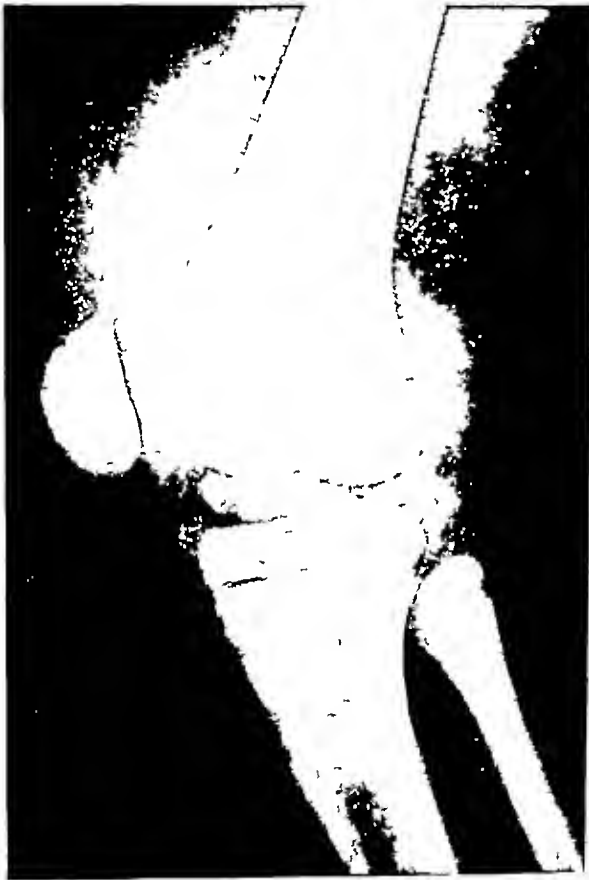
Still a third fracture mechanism has been described by Jones and Smith⁶ and quoted by numerous authors. It occurs relatively seldom and has not appeared in Clarke's⁹ series nor in our own. In these cases, the lateral spine of the tibia may be fractured without avulsion if the lateral femoral condyle smashes medially against it. Such an event is more apt to occur in association with fractures of the tibial condyles, or when the collateral ligament is stretched or torn. It can only take place when the lateral tibial spine is longer or sharper than usual, and Jones and Smith⁶ showed that there is a wide disparity of skeletal development in this respect. In dissection, Jones was able to demonstrate

of injury followed by swelling and hemarthrosis, with pain in the knee joint and inability to extend the knee. In the acute stage it is doubtful if this type of locking can be distinguished from that of a torn cartilage, though Jones describes a difference in the feeling of bony resistance.

Certainly, this sign cannot be relied upon completely, and in one of our cases the similarity was great enough to deceive us as described below. The outstanding clinical picture is that of "internal derangement," and the surgeon who sticks to this diagnosis will find it the most discreet as well as the most euphonious pronouncement he can make in the early stages. Roentgenography will, of course,

checks excessive inward rotation of the tibia on the femur. If the body weight is thrown backward at a time when the knee is bent, with the tibia pressing forward, the full force will be exerted against the attachment of the anterior cruciate ligament, and it is here that the lock of the handcuffs will break open if fracture occurs. As it does so, the soft bony fragment to which it is attached jerks

He reproduced all these injuries by forcing the tibia violently forward in relation to the femur, or by reversing the blows, and forcing the femur backward in relation to the tibia. He cited a most interesting case reported by Ross,⁶ in which these mechanical forces had accidentally been given a clinical demonstration. This occurred when a heavy block, which was secured under tension by a cable, tore



A



B

FIGURE 2 Roentgenograms of N. C.

Views before and after reduction by manipulation, showing upward displacement of the anterior cruciate insertion

upward, leaving a punched-out depression in the superior surface of the tibial articulation.

A particularly interesting study of the pathomechanics of this fracture was presented in 1922 by Blaisdell⁵ in connection with experiments performed on cadavers. He worked out what he called the "crucial triad," representing the three types of injury that might follow undue strain on the anterior cruciate ligament. The first was avulsion of the osteochondral fragment at its insertion, as already described, the second, rupture of the cruciate ligament itself, and the third, avulsion of the attachment of the ligament from its point of origin on the inner side of the lateral femoral condyle

loose and catapulted against the back of a man's calf, just below the knee. By good luck, the man was wearing high rubber boots, rolled down at the knee, which had the effect of dispersing the force and which protected the skin from compounding Callender's⁷ old, and not always reliable, rule that "bone gives way before fibrous tissue" was borne out in this case, for the final injury sustained was an avulsion fracture of the anterior cruciate attachment.

In addition to the back-and-forth strain, it must be remembered that avulsion fractures of the anterior cruciate ligament may be caused by inward rotation of the tibia, producing a simple twist of

to the side of the tibial tubercle. The bit emerges in the floor of the cavity from which the bony fragment was avulsed. A second hole is drilled parallel to the first and No. 2 chromic catgut is then threaded up through one hole, matted through the fragment and brought down through the other hole to be tied over the tibial bridge (Fig. 3). Any alternative method of fixation would probably be equally effective, and Roth¹ has even stated that no fixation is necessary, once the fragment has been reduced and the leg secured in extension. Certainly greater security can be felt after the joint is opened if the surgeon has anchored down his reduction with some form of fixation. A stovepipe plaster is then advisable for not less than three weeks, after which gradual knee motion should be resumed actively.

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CASE 2. N. C., a 15-year-old boy, was thrown from his bicycle and was brought to the hospital with his left knee in about 15° flexion. He was unable to extend it or to bear weight. He could flex the knee to 90°. An attempt to test the cruciate ligaments proved so painful that it was not carried out in full. X-ray films revealed elevation of the anterior spine of the tibia, together with a moderately large fragment from the upper tibial epiphysis. An attempt was made to reduce this fracture under anesthesia. Full extension could not be obtained until the operator placed his right and left thumbs on either side of the patellar tendon and pressed in deeply as he manipulated the knee toward extension. A sudden snap was then felt, giving the impression that this misplaced fragment had been reduced. Full extension could then be easily obtained, and in this position a long leg cast was applied. The patient's postoperative course was uneventful. He was allowed on crutches on the 4th hospital day and was discharged on the 10th day, to be followed in the Out-Patient Department. The cast was retained for 3 weeks, after which he was allowed to walk on crutches without weight bearing. On his last visit, at the end of 3 months, he showed full, normal range of motion, and stated that he had no disability whatever. He was not limited in any way in his activity, and he had no pain.

CASE 3. C. W., a 29-year-old man, fell about 20 feet from a ladder and landed on his feet. At first he did not realize that he had been injured, but after 30 minutes there was a dull pain in the right knee, and he was unable to extend it fully. After 8 days, he came to the hospital. Flexion to 90° was readily obtained, but extension beyond 165° could not be carried out without severe pain. The patient localized his pain in the anterior compartment just behind the patellar tendon. X-ray films were regarded as normal though subsequent examination revealed the fracture with very slight displacement on the lateral view and none on the anteroposterior view. The patient was operated on under the diagnosis of probable torn cartilage. The anterior cruciate ligament with the tibial spine and a portion of the adjacent tibial plateau were found avulsed in a roughly quadrangular manner, and displaced upward into the anterior compartment of the knee. A tunnel suture was carried out by the technique described above. A plaster cast was applied, and postoperatively x-ray films showed the fragment in good position,

with normal joint space. The patient proved particularly unco-operative, and in spite of all efforts, he persisted in keeping the knee rigid after the cast was removed at the end of 4 weeks. This continued for 3 months, and resulted in an almost completely stiff knee. Manipulation under anesthesia at the end of this time succeeded in flexing the knee to 90° without difficulty, but it is estimated that another 3 months will be required before normal motion is regained.

CASE 4. A. M., a 46-year-old man was injured while shoveling dirt from the bottom of an 8-foot trench when the ground caved in and buried him up to the level of his knees. While he was thus immobilized, a chunk of tarred surface, about 75 pounds in weight, skidded against his thigh so hard that he was thrown in a semicircle to the left and backward while his legs were still firmly planted in the gravel. After being freed, the patient was unable to walk, and his knee was swollen. X-ray examination revealed a fracture of the anterior tibial spine of the left knee. The knee could be fully extended without anesthesia, and a plaster cylinder was applied in this position. Quadriceps-setting exercises were permitted while the leg was in plaster. The cast was removed after 1 month. At the end of 12 weeks the patient walked with a slight limp. He still lacked 5° of full extension. Flexion was normal. After 16 weeks, there was no loss of extension or flexion, but some degree of quadriceps atrophy was still present.

CASE 5. P. A., a 14-year-old girl, was knocked off the bicycle that she was riding, and when her right foot struck the ground there was immediate pain in her right knee. In the course of the next few hours, the knee became markedly swollen, and she was unable to extend it. She was given a general anesthetic, and her physician manipulated the knee so that extension was obtained. After consultation an x-ray examination disclosed an avulsion fracture of the tibial spine, and the knee was then immobilized in a plaster cylinder in the position of extension. At the end of 6 weeks weight bearing was permitted, and after 10 weeks there was only slight residual swelling and tenderness over the anterior compartment. She exhibited full flexion, but lacked 5° of full extension. She has since regained full extension, and she walks and dances without any trace of disability.

SUMMARY

The mechanism and treatment of fractures of the tibial spines are discussed, with a review of the literature, and 5 cases are presented.

Conservative treatment by closed manipulation, followed by a cylinder cast, is recommended in all but the exceptional cases. The technic of open and closed reduction is described.

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reveal the bone injury, but even here, caution must be observed. In the anteroposterior view, the displacement may hardly be noticeable, and in the lateral aspect, the avulsed portion may not offer heavy enough calcification to be at all conspicuous unless the films are of good quality and are studied with care. A hazy film will often be misinterpreted, but in a good film the osteochondral fragment can be clearly seen lifted from its bed in the tibial plateau (Fig. 2).

CLOSED REDUCTION

Treatment of anterior-spine fractures may often be very simple. In cases in which displacement is slight, or in which there is no displacement, nothing is required except a stove-pipe plaster cast well applied. Theoretically, this does not wholly limit rotation of the tibia on the femur, but complete immobilization does not seem to be necessary. The cast should be maintained for five to seven weeks, depending on the severity of the injury.

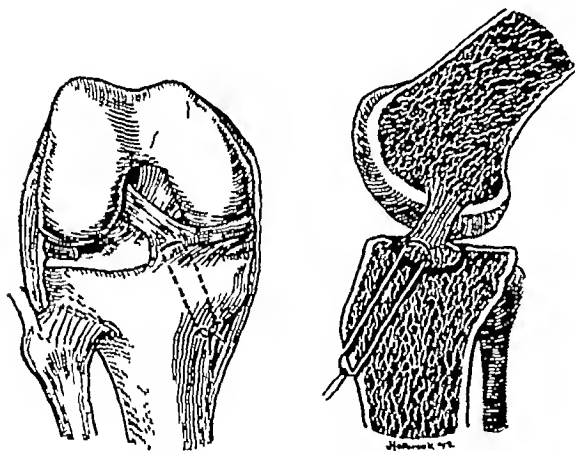


FIGURE 3 Tunnel Suture of Insertion of Anterior Crucial Ligament

During this interval full weight bearing should be encouraged. In the more severe cases, in which the avulsed fragment has broken loose so that it is tilted upward into the knee joint, a general anesthetic must be given, but here, again, the fragment can usually be manipulated back into place by simple extension of the lower leg. If the displaced fragment fails to respond to this maneuver, Clarke⁹ has described the use of gentle rotation of the tibia on the femur to stretch the crucial ligament and thus to disengage the bony fragment, after which extension of the knee serves to complete the reduction. An even more forcible maneuver may sometimes be required, as in Case 2. Here it was necessary for the operator (H. K. M.) to press with both thumbs on the two sides of the patellar tendon until he felt he was able to catch the edge of the

fragment and depress it enough for it to fall back into place when the knee was extended.

OPEN REDUCTION

Although most authors believe that closed manipulation will succeed in reducing these fractures, Roth¹ has insisted upon open reduction. His reasons would seem more convincing if they were not controverted by the general experience of many other surgeons. He believes that the anterior attachment of the lateral meniscus is displaced by the avulsion in such a way that it folds under the bony fragment and obstructs reduction. "From my experience at operation," he says, "it is clear that what prevents the fragment from being replaced is the lateral meniscus. Until this is divided, no replacement is possible." That this cannot be true is proved by the fact that Clarke was able to reduce all 10 of the cases in his series by simple, closed methods. "Extension under anaesthesia will always reduce the fracture," he states, and again, "we have never found it necessary to resort to operative treatment." Four of our cases confirmed Clarke's dictum, and in the fifth, which we opened under a mistaken diagnosis, we found the avulsed fragment lying free, with the meniscus offering no impediment to reduction. Nevertheless, Roth's observation should be borne in mind, for it will explain failures in reduction that might occur.

MacAusland¹⁰ and Lee¹¹ have argued in favor of open reduction on the grounds that the fragment can be replaced more accurately, the fixation will be more secure, and recovery will be more speedy. In their postoperative care, plaster casts are maintained for three weeks as against five to seven weeks by the nonoperative technic. The formidable risk of wide surgical exposure of a knee joint does not seem to us to justify the small advantage gained by this operation in routine cases. Nevertheless, each surgeon will judge for himself. Sever¹² observes: "I am not at all convinced that early operation for repair of that particular type of fracture (tibial spine) is necessary, wise, or even efficient, and I don't think the results are as good and the risks certainly are greater."

For a surgical approach our own preference is for the parapatellar type of exposure, with the original incision beginning as in a simple knee-cartilage operation, and with extension of the incision as much as may be needed.

Once the joint has been opened, the semilunar cartilage should be inspected and if damaged removed. The tibial avulsion itself can usually be replaced with ease. Lee¹¹ has advocated suturing it in place, and MacAusland¹⁰ has recommended screw fixation. Compere's fracture textbook illustrates the method of drilling a tunnel and suturing, which we have found to be both useful and easy. A bit is drilled obliquely upward from a point about 2.5 cm beneath the tibial plateau and 1 cm

to the side of the tibial tubercle. The bit emerges in the floor of the cavity from which the bony fragment was avulsed. A second hole is drilled parallel to the first and No. 2 chromic catgut is then threaded up through one hole, matted through the fragment and brought down through the other hole to be tied over the tibial bridge (Fig. 3). Any alternative method of fixation would probably be equally effective, and Roth¹ has even stated that no fixation is necessary, once the fragment has been reduced and the leg secured in extension. Certainly greater security can be felt after the joint is opened if the surgeon has anchored down his reduction with some form of fixation. A stovepipe plaster is then advisable for not less than three weeks, after which gradual knee motion should be resumed actively.

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OTOLOGIC ASPECTS OF VERTIGO*

JOSEPH J FISCHER, M D †

BOSTON

VERTIGO is a very important word in the vocabulary of the otolaryngologist. Unfortunately, some confusion exists, regarding not only etiology but also definition and nomenclature. One has to bear in mind that vertigo is a subjective symptom that makes the physician entirely dependent on the history given by the patient, who may call the most variegated sensations vertigo. He not only describes the feeling of being turned around or of objects turning around, but also sensations of losing the ground or being lifted up, or lightness or heaviness in the head. Others complain of unsteadiness and fainting, and finally a great many call vertigo the various visual sensations such as blurring, double vision, jumbling of letters and vertical lines that appear oblique.

Hence the confusion in the nomenclature: turning vertigo, tactile vertigo, ocular vertigo, spatial vertigo, epileptic vertigo, hysterical vertigo, cardiac vertigo and so forth.

The same confusion holds for the numerous definitions of vertigo, some based on physiologic processes, and others on psychologic ones.

Vertigo can be elicited by all organs concerned with spatial consciousness: the peripheral labyrinth, central pathways, eyes and proprioceptive pathways. For the last, attention should be directed to the close relation of the labyrinth to the tonus of the body musculature.

For the otolaryngologist the two important questions pertaining to vertigo are whether labyrinthine and nonlabyrinthine vertigo can be differentiated, and whether, within the labyrinthine vertigo, the central and peripheral types can be differentiated.

Considering the fact that vertigo is not an objective symptom that can be ascertained by the physician or determined quantitatively like other functional tests and that there is no histologic proof for the anatomic pathways, it appears obvious that such a differential diagnosis cannot be made on a scientific basis. The question must therefore be approached from a clinical point of view based upon clinical experience of thousands and thousands of cases, hence the differential diagnosis must always be considered a tentative one. There is first the differentiation of labyrinthine and nonlabyrinthine vertigo. The former is rotational, directional or systematic, the latter is nonrotational, nondirectional and asystematic. The latter group comprises the various sensations of dizziness found in diseases of the cardiovascular system and the gastrointestinal tract, endocrine lesions, visual disturbances and

so forth. It is discussed in detail from the standpoint of internal medicine by Dr. Aisner.

Table 1 summarizes the differentiation of peripheral labyrinthine vertigo and central vertigo.

When one is taking the history of a patient with vertigo all leading questions must be strictly avoided, but if the patient himself mentions turning sensations spontaneously, his statement is of great importance.

Sham movements of surrounding objects are much more common than similar movements of the subject, the direction of the sham movements is the same as the fast component of the nystagmus.

Peripheral vertigo occurs in the form of attacks, such a spell usually lasts a minute or a few minutes. There are but few exceptions in which the attack may continue for hours with a peripheral lesion. Examples of this type are rupture of the window, hemorrhages and trauma. The clinical importance of a thorough history is demonstrated by the case of a patient with a chronic otitis media who has had repeated attacks of vertigo off and on over a long period. However, there is one spell he will never forget, he knows the exact date, even the exact hour when it occurred, and he knows also the direction of the moving objects. Such a history enables the clinician to arrive at the diagnosis of fistula of the horizontal semicircular canal, the establishment of the fistula coincides with this one severe attack of vertigo.

Peripheral vertigo is often brought about by sudden changes of the position of the head. It is a characteristic history when the patient complains about his first attack in the morning when he gets out of bed, it is the change from the recumbent to the vertical position. The second attack occurs when he washes his face, there again is the change of position when he bends his head.

Consciousness is never absent in peripheral labyrinthine lesions regardless of the intensity. Even with the most violent attack of vertigo, as mentioned above (window rupture), the patient will never lose his consciousness. Hence a loss of consciousness reported by the patient points rather toward a central lesion.

Spontaneous nystagmus is always present during an attack of vertigo caused by peripheral labyrinthine lesions, outside the spells, nystagmus may or may not be present, according to the underlying disease.

The course of peripheral labyrinthine vertigo is self-limited. In cases of labyrinthitis there exists in the beginning vertigo and nystagmus to the affected ear, increasing in intensity, with the destruction of the labyrinthine function, vertigo disappears (limited course). Should, however, the

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infection spread beyond the boundaries of the inner ear, vertigo and nystagmus recur (now in the opposite direction), enabling the clinician to arrive at the diagnosis of meningitis of the posterior fossa, or cerebellar abscess. In central lesions vertigo starts, gradually increases in the further course and persists usually for the entire length of time.

The caloric reaction influences the spontaneous vertigo in cases of peripheral labyrinthine disease, whereas central lesions may not reveal any influence or some disproportion may exist between induced vertigo and induced nystagmus.

Disturbances of equilibrium in labyrinthine diseases show the character of the peripheral type—

Postconcussion states, both simple and complicated

Sea sickness and air sickness

Cardiovascular lesions showing either rotational vertigo as in vasomotor lesions of the end arteries, thrombosis of the inferior cerebellar artery and arteriosclerosis or nonrotational (described by Dr Aisner)

Vertigo can easily be understood as a symptom in such peripheral diseases as inflammatory, degenerative, toxic and traumatic conditions. It may however be difficult to explain the mechanism of vertigo for a number of lesions commonly summarized under the heading of vascular disturbances.

TABLE I Differential Characteristics of Peripheral Labyrinthine and Central Vertigo

TYPE OF VERTIGO	TURNING SENSATION	SPINAL MOVEMENTS OF SURROUNDING OBJECTS	OCCURRENCE OF VERTIGO	INITIATED BY MOTION	LOSS OF CONSCIOUSNESS	NYSTAGMUS	COURSE	AFFECTED BY CALORIC TEST	DISTURBANCE OF EQUILIBRIUM	SPONTANEOUS NYSTAGMUS	OTOSCOPIC FINDINGS	NEUROLOGIC FINDINGS
Peripheral labyrinthine	Rotational	Present	In attacks	Yes	None	Present	Self-limited	Yes	Peripheral type	Peripheral	Often positive	Negative
Central	Rotational lateropulsion	Absent	Continuous	No	Occasionally	Often absent	Persistent	No necessarily	Central type	Central type	Negative	Often positive

that is, falling in the direction of the slow component and changes in falling with changes in the position of the head. In central lesions the equilibrium shows disturbances of the central type—that is, independently of the position of the head.

Spontaneous nystagmus in labyrinthine lesions shows the peripheral type associated, horizontal-rotatory or rotatory-horizontal, medium in amplitude and frequency, and persistent. In central lesions the spontaneous nystagmus may be associated or dissociated, plain horizontal or rotatory or vertical, coarse in amplitude, slow in frequency and persistent or transient.

The otoscopic findings in peripheral diseases are often positive, such as acute or chronic otitis media, cholesteatoma, adhesive process and scars, whereas in central lesions the findings are usually negative.

The neurologic findings in peripheral diseases are mostly negative, whereas in central lesions they are often positive.

The following diseases are accompanied by vertigo

Labyrinthine and retrolabyrinthine disorders, including inflammatory, degenerative, toxic, traumatic, neoplastic and vascular lesions (Ménière's syndrome, angioneurotic crisis, allergy, migraine).

Central lesions particularly fast developing (inflammations, hemorrhages, multiple sclerosis—acute stage—and tumors) which display marked vertigo, whereas slowly developing processes such as multiple sclerosis, syringobulbia, chronic processes and slowly growing tumors show very little or no vertigo.

Ménière's syndrome is the most important in this group. A few of the many theories comprise disturbances of water, sodium or potassium metabolism and allergy as a basis of the lesion. In spite of the apparent contradiction all these theories assume more or less the same origin—namely, a retention of fluid, leading to extracellular edema. Since the labyrinth presents a cavity with stiff walls filled with fluid, the slightest cellular edema will raise the endolabyrinthine pressure. This, in turn, explains the attacks of vertigo, the tinnitus and the impaired hearing.

Angioneurotic crisis of the eighth nerve was first described by Kobrak¹. He assumed an increased permeability of the vessels of the labyrinth and of the choroid plexus. The clinical manifestations are almost the same as those in Ménière's syndrome.

Hyperactivity of the *carotid-sinus reflexes* was given by Soma Weiss² as a cause of clinical symptoms such as periodic attacks of vertigo, vasospasm, intestinal cramps and allergic reaction.

Allergy as a basis for the Ménière syndrome has long been assumed by many authors. The fact that elimination of certain foodstuffs improved the clinical condition and that the histamine skin test (Miles Atkinson³) was positive gives proof that at least some cases are allergic in etiology.

Migraine otique is the name given by Escat⁴ to the following clinical pictures: attacks of vertigo, spontaneous nystagmus, tinnitus, impaired hearing, headaches and hemianopsia. The underlying lesion has been described as a circulatory disturbance of the internal auditory artery, increased endocranial pressure or brain swelling.

In central lesions differentiation should be made between fast developing and slowly developing diseases. Although the former are always associated with vertigo, the latter show very little or no vertigo. The majority of otolaryngologists believe that vertigo is a frequent symptom of multiple sclerosis. This is an erroneous assumption since vertigo is only experienced in cases of acute exacerbations of multiple sclerosis.

In simple *post-concussion* lesions vertigo is often the only symptom, lasting for many years. It is very difficult for the otologist to answer the question whether vertigo is caused by an organic lesion, or whether it is of psychogenic origin. Positional nystagmus and the head-moving test are suggestive.

In the complicated post-concussion lesion — that is, *commotio cerebri* in addition to fracture of the skull — some other symptoms, such as headaches, fatigue, deafness or impaired hearing and tinnitus, are present.

In *sea sickness* and *air sickness* vertigo is associated with vasovegetative symptoms such as nausea, vomiting, perspiration, pallor, salivation and even diarrhea. The peripheral labyrinth is generally claimed as the site of the lesion. The observation that deaf mutes without labyrinthine function are not subject to sea sickness and the fact that sea sickness can be produced experimentally by imitation of the exact movements of the ship seem to favor this theory. However, there is one main symptom missing — namely, spontaneous nystagmus, which is characteristic of peripheral labyrinthine lesions. One theory explaining the lack of spontaneous nystagmus is propounded by Quix,⁵ who

assumes that sea sickness is caused by stimulation of the otolith apparatus.

In cardiovascular lesions one must differentiate the directional or true vertigo and the nondirectional or vague dizziness. To the former group belong the vasomotor disturbances of the internal auditory artery. It is difficult to locate the site of the vertigo, whether the peripheral labyrinth or the central labyrinthine pathways are involved. The same difficulty holds true for cases of thrombosis of the inferior cerebellar artery. Shuster⁶ describes a syndrome consisting of vertigo, loss of hearing of high-pitched tones and involvement of the vertical semicircular canals. He assumes arteriosclerotic changes of the artery supplying the vertical canals and the part of the cochlea concerned with the perception of high sounds.

For a detailed study on rotational vertigo the reader is referred to the book "The Inner Ear" by Fischer and Wolfson⁷ and for all the other forms of dizziness in cardiovascular and other diseases to the discussion of vertigo from an internal point of view presented by Dr. Aisner.

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NEUROLOGIC ASPECTS OF VERTIGO

DEREK E. DENNY-BROWN, M.D.*

BOSTON

VERTIGO is a sensation, a symptom without any essential objective sign, and is therefore subject to all the limitations imposed by the descriptive powers and capacity for observation possessed by the patient. It is a subjective sensation of dis-equilibration and, whatever its origin, may be accompanied by nausea, vomiting and circulatory collapse when the vertigo is severe. It is obviously important to separate the symptom from the sense of uncertainty, often described as dizziness ("false vertigo") complained of by psychoneurotic patients, particularly in panic states, but this is in practice not difficult. The distinguishing characteristic of true vertigo is that the sense of apparent movement is consistent, occurs in clear-cut attacks and is made worse by movement.

The neurologist is chiefly interested in the decision whether a given complaint of vertigo has

origin in the labyrinth, the brain stem or the cerebrum. He is but little concerned with ocular causes, for they do not present vertigo as a primary disorder, and in such conditions as carotid-sinus syndrome and anemia the vertigo is usually non-specific and not a leading symptom. In the decision of the three usual situations of origin of true primary vertigo, the chief criteria used by the neurologist are the type of sensation, the form of the attack and the associated symptoms.

The type of sensation is infinitely variable. In the most clear-cut sensations of rotation, the direction of movement of objects should indicate the side of the lesion. A sinking sensation has no special significance, though its association with sudden limpness of the limbs may indicate involvement of the saccule or utricle ("the otolithic catastrophe" of Tumarkin[†]). Whether the patient feels that he

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†Tumarkin A. Otolithic catastrophe: new syndrome. *Brit. M. J.* 2:175-177, 1936.

rotates or objects rotate around him has not been found of any value in the differential neurologic diagnosis

The most important criterion in my view is the *form of the attack*. Vertigo of labyrinthine origin is paroxysmal, beginning suddenly and maximally and then subsiding gradually. The attack should be brief—that is, lasting minutes or perhaps an hour or two—and should leave only a minor residual sensation of slight movement. Vertigo resulting from brain-stem lesions is by contrast more continuous, is made worse by movement and persists for hours or days at a time. Vertigo may occur at the beginning of an attack of epilepsy or migraine but is then transient, and does not persist after the remainder of the attack. If labyrinthine vertigo is sufficiently severe to be associated with other symptoms it outlasts them. Both peripheral and central vertigo may be related to change in posture, but, in my experience, this is more common in the central form.

The usual associated symptoms of peripheral vertigo are tinnitus and deafness, but these may be entirely absent for a long period after the first attacks of Ménière's disease. The most common associated symptoms of vertigo from brain-stem lesions are diplopia and other disorders of the cranial nerves such as numbness of the face, dysarthria and ataxia. I have seen loss of consciousness from peripheral vertigo, but only as syncope at the height of a very severe attack. It is also uncommon in central causes, except in epilepsy with vertiginous aura. If headache and vomiting are the first symptoms, a central cause must be suspected.

The neurologic disorders associated with vertigo are chiefly diseases of the brain stem. Tumors of the lateral recess (auditory neuromas) and cere-

bellar tumors are associated with vertigo only in about 50 per cent of cases. Distortion of the brain stem is then present. Multiple sclerosis is associated with vertigo when a recent patch of the disease involves the brain stem, with associated cranial-nerve palsy, ataxia and disorder of the long tracts, but the vertigo subsides with the end of the acute phase of the attack. Thrombosis of the posterior inferior cerebellar artery is also a cause, and occlusion of other vessels in the pons and medulla gives rise to transient episodes of vertigo and cranial-nerve palsy in patients liable to vascular disease. Chronic syphilitic meningitis can produce a characteristic syndrome of facial paralysis, deafness and vertigo from loculation in the lateral recess.

The investigation of vertigo involves not only a careful history and a close examination of labyrinthine function but also testing of the other cranial nerves. If weakness, numbness or ataxia of limbs is present the patient has usually complained of them. The best leads to a correct appreciation in a doubtful case are always to be gained from the history.

Treatment of the condition obviously depends upon the diagnosis. I have nothing to add that is not already common knowledge, but wish to emphasize the commonly remitting character of Ménière's disease, and the value of tiding over early attacks with small doses of phenobarbital. In my opinion, the more radical treatments have many disadvantages and should not be embarked upon unless the patient's livelihood is at stake and the condition clearly one-sided. Finally, I would warn against leaping to the conclusion that the patient is psychoneurotic simply because he is overanxious. A continuous uncertainty concerning the next moment when one may be flung to the ground can unnerve anyone.

VERTIGO AS IT CONFRONTS THE INTERNIST

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BOSTON

THE term "vertigo" has been subjected to a great deal of abuse. It is not synonymous with "dizziness," which is an extremely common symptom encountered almost daily by the practitioner of general medicine. Vertigo implies a sense of rotation with reference to surrounding objects in space and a loss of the sense of equilibrium. The patient complaining of this symptom is aware of some difficulty in the postural mechanism, and has a feeling of insecurity, especially in the upright position, when a sensation of falling or veering to one side is present. It is often a disabling and alarming symptom, and one for which the patient will almost invariably seek medical attention. When resulting from disease involving the peripheral

labyrinth or auditory nerve, it is associated with tinnitus and deafness.

In contrast are a group of subjective manifestations variously referred to by the patient as dizziness, lightheadedness, giddiness, faintness, swimming sensation, fog before the eyes, blackout and so forth. Such symptoms are often seen in a variety of functional and organic disturbances, and should be differentiated from what is considered true vertigo. Differentiation is made possible by an accurate description of the sensations experienced by the patient, and by the evaluation of associated symptoms and underlying or predisposing conditions. From the standpoint of the internist, these subjective complaints are far more frequently encountered than true vertigo. Thus, they may comprise

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part of the symptomatology of neurosis, cerebral arteriosclerosis, hypertension, various other cardiovascular disorders, endocrinopathies, infectious diseases, gastrointestinal disturbances, sudden changes in posture, blood loss, other conditions causing cerebral ischemia and so forth

Perusal of many of the modern textbooks of medicine readily demonstrates the common misuse of the term vertigo, when actually the subjective sensation of dizziness or one of its many equivalents is meant. Thus, vertigo is listed as a symptom of a host of medical ailments, among them cardiac arrhythmias, heart block, cardiac failure, carotid-sinus syndrome, hyperthyroidism, hypoglycemia, Addison's disease, anemias, menopausal syndrome and gastritis, to mention only a few. True vertigo is generally not encountered as part of the symptomatology of these disorders. Dizziness and its many variants, however, are quite common.

Apart from pure neurologic and otologic entities, the internist is apt to see vertigo as a manifestation of one of the following: hypertensive cardiovascular disease, leukemia and drug intoxication.

Occasionally, one encounters mild vertigo in patients with hypertensive cardiovascular disease, more commonly in women. It may be associated with tinnitus. In unusual cases the vertigo and tinnitus may occur as isolated severe attacks, and under such conditions may be mistaken for Ménière's syndrome. Such patients usually present a history of attacks after periods of excessive physical activity. Less commonly, in hypertension associated with arteriosclerosis, hemorrhage into the labyrinth may result in the sudden onset of severe vertigo, tinnitus and deafness.

Involvement of the middle ear, the internal ear and the auditory nerve in the acute and chronic leukemias, though uncommon, is well known. The pathologic processes include hemorrhage, leukemic infiltration and connective-tissue proliferation. Symptoms of vertigo, tinnitus and deafness result.

Intoxication with drugs such as quinine, quinidine, cinchophen and the salicylates may produce the symptoms of vertigo, tinnitus and decreased auditory acuity. This has been attributed to func-

tional impairment of the eighth nerve. The administration of streptomycin has frequently resulted in vestibular dysfunction and less commonly in deafness. The occurrence of such disturbed function is related to both the size of the dose and the duration of treatment. More recently, with the accepted lower dosage schedules for the treatment of streptomycin-sensitive infections, less difficulty with labyrinthine function has been experienced. However, patients on the same dosage of the drug differ considerably in their susceptibility to these so-called toxic manifestations. The rotary component of vertigo is often absent in these persons, although difficulty with the postural mechanism is characteristic. Frequently, they experience the sensation of overshooting the mark when a sudden movement is made. For example, in reaching for an object, the hand may continue its progress for several inches beyond the object, or rolling over in bed may convey the sensation of continuation of that act. The pathologic changes resulting in these symptoms have been localized by some to the ventral cochlear and inferior cerebellar nuclei, although recently additional disturbance in the peripheral mechanism has been postulated.

Vertigo not attributable to any of the causes already discussed falls into the realms of the neurologist and otologist, and may be a manifestation of disease of the labyrinth, the brain stem or the cerebrum. Under such circumstances, the internist, who is apt to see these cases first, must seek proper consultation. A history of recurring episodes of vertigo associated with fluctuating tinnitus and deafness may indicate Ménière's syndrome, which the internist may take upon himself to treat. In patients presenting vertigo as a symptom for the first time, consultation seems in order. Careful history taking and physical examination may be of value in the choice between neurologist and otologist. For example, persistent and progressive vertigo, disturbances in consciousness, memory defects and the presence of cranial-nerve palsies point to a lesion in the central nervous system and the advisability of neurologic consultation. The details of the otologic and neurologic aspects of vertigo have been discussed by Drs. Fischer and Denny-Brown.

THROMBOCYTOPENIC PURPURA ASSOCIATED WITH TUBERCULOUS SPLENOMEGALY AND TUBERCULOSIS OF THE BONE MARROW*

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PHILADELPHIA

WHEN splenectomy in thrombocytopenic patients has on occasion revealed the tuberculous origin of a splenic enlargement, the post-operative results have been dramatic. Surgical intervention has removed both a fatal tuberculoma and a serious blood dyscrasia.^{1,2} Further knowledge of this apparently rare combination will probably show that such a surgical cure is not to be anticipated in every case because of developments such as those reported below—namely, the association of “primary” tuberculosis of the spleen, thrombocytopenic purpura and a widespread tuberculosis of the bone marrow. We are unable to find a similar grouping of such lesions which almost certainly was the basis for the fatal thrombocytopenic purpura in the following case.

CASE REPORT

R. A., a 51-year-old Negro inmate of the Eastern State Penitentiary previously in good health, complained on August 5, 1947, of lumbar pain radiating toward the right buttock and posteriorly down the right thigh. Also he stated that he had lost 25 lb. (the weight dropping from 195 to 168 lb.) in 5 months.

Physical examination revealed a hypertensive status but was otherwise negative. Later the sciatica disappeared but pain appeared in the left upper quadrant of the abdomen. Attention was further drawn to the patient's complaints when a tonsillectomy was postponed because of a bleeding time of 30 minutes. On November 26, 1947, re-examination disclosed that the spleen was palpable and very firm; the prostate was enlarged and hard but elastic. X-ray examination of the chest and pelvis did not reveal pulmonary or bone disease. The prostatic enlargement was diagnosed as hypertrophy of the prostate.

Fever and prostration developed in the latter part of November and from then until death on January 14, 1948, the temperature showed a septic fluctuation ranging from 96 to 102°F. The red-cell count remained fairly stable ranging from 4,200,000 to 5,850,000 but early in January, in spite of a transfusion of 600 cc. of blood and continuous iron and liver therapy, the count dropped sharply. On January 11 examination of the blood showed a red-cell count of 5,000,000 and a white-cell count of 8900 with 78 per cent neutrophils, 21 per cent lymphocytes, 1 per cent myelocytes and occasional normoblasts. The platelet count was 100,000. Another platelet count and a bone-marrow biopsy were ordered but unfortunately could not be done. The lungs remained clear. The liver was enlarged, and the spleen extended down to the umbilicus and was slightly tender. Increasing hemorrhages from the nose and mouth, perineal eruptions on both arms and the presence of numerous erythrocytes in the urine preceded the patient's death.

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An autopsy, performed by Drs. Charles Swalm and Benjamin Gouley at the Coroner's Office of Philadelphia, the conjunctivas showed moderate icterus; purpuric spots were visible on the arms and the trunk in spite of the dark skin; a black bloody secretion was present in the nose and mouth.

The lungs were normal aside from terminal congestion and edema. The liver was large, pale and soft, with numerous milium tubercles beneath the capsule and throughout the parenchyma. The spleen was greatly enlarged, weighing 950 gm. The capsule was roughened and nodules milium.



FIGURE 1. Conglomerate Caseous Tuberculosis of the Bone Marrow (from the Middle Portion of the Sternum).

Large cell dark stained is seen at 10x, in small adjacent tubercle. Bone trabecula is seen at lower left (x 200).

and larger were visible through it. Section showed pale-yellow caseous nodules ranging in size up to a nail dollar. The intervening pulp was dark and so.

The stomach and small intestine were filled with dark blood. The adrenal glands were normal as was the pancreas. A few scattered milium tubercles were noted in the cortex of the left kidney. The urinary bladder showed congestion of the mucosa over the trigone with some small tubercles. The right lobe of the prostate was enlarged to the size of a lemon and filled with large caseous nodules conglomerate with caseation in the adjacent seminal vesicle.

No bone lesion was noted on gross examination. However on decalcification of numerous bone sections preparation for histologic examination it was noted that the marrow substance showed grayish-white infiltrations, generally small and patchy but in some areas solid, homogenous and waxy.

Death was due to massive gastrointestinal hemorrhage in connection with a widespread purpura. His pathological examination of the liver disclosed numerous milium tubercles. The intervening parenchyma showed an inflammatory reaction. The Kupfer cells were swollen and the liver cords separated in many fields by edema.

into which many polymorphonuclear leukocytes had infiltrated. The periportal tissue also showed a cellular infiltration composed of many monocytes and polymorphonuclear leukocytes, but there was no increase of fibrous tissue and no biliary-duct hyperplasia.

The spleen showed extensive caseation. There was a marked hemorrhagic infiltration around most of the caseous areas, infiltrating them, undergoing an acute hyalinization and merging in many fields with the caseation. The splenic follicles were not hyperplastic, but there was a moderate reticuloendothelial hyperplasia lining the sinusoids. The latter contained erythrocytes and monocytes of various types. No megakaryocytes were found.

Sections from three ribs (fourth, fifth and sixth left, adjacent to the costochondral junction) and from the mid-portion of the sternum all showed widespread miliary-tubercle invasion, and marrow hyperplasia in the intervening non-caseous areas. Conglomerate caseation replaced the original marrow structure in many low-power fields in sections from each of six paraffin blocks (Fig. 1). Typical giant cells of the Langhans type were numerous and were found even in the small submiliary foci of early caseous coalescence (Fig. 2). Although numerous tubercles impinged on the bony trabeculae, the latter were scarcely involved. In many areas they remained undamaged despite the complete disappearance of the marrow and its replacement by caseation. In only

the center and the periphery of the cell. Other giant cells showed a peculiar ring-shaped deposition of the chromatin (Fig. 3). They were remote from caseous areas, and could be differentiated from the Langhans giant cell of caseation by their structural and staining aspects. They were considered to be degenerate megakaryocytes.

Staining for acid-fast organisms in paraffin sections revealed well stained tubercle bacilli in the caseous lesions of the spleen,

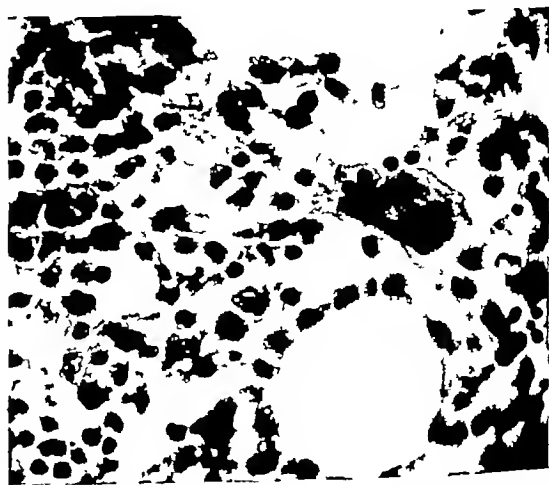


FIGURE 3 *Megakaryocyte, Degenerate Form (?), with Large Giant Cell, Remote from Caseous Lesions and Clear Basophilic Cytoplasm.*

Note marrow hyperplasia with numerous normoblasts ($\times 500$).



FIGURE 2 *Coalescence of Small Miliary Tubercles. Note the characteristic giant cells of Langhans type. The dark curved upper border is a bone trabecula ($\times 176$).*

one or two fields was there characteristic fragmentation under osteoclastic attack.

In the bone-marrow hyperplasia, erythropoiesis predominated. Megaloblasts and especially normoblasts crowded the fields. Granulopoiesis was rather diminished, and in some fields scarcely noted. Normal megakaryocytes were absent. However, there were many large giant cells, irregularly round, with clear basophilic cytoplasm. They contained a hyperchromatic nucleus of varied shape, generally, it was a tangled skein of dense black structure covering both

the prostate and seminal vesicle, and numerous but poorly stained bacilli in the bone marrow.

DISCUSSION

Purpura has long been recognized as an occasional complication of pulmonary and nonpulmonary tuberculosis.³⁻⁵ Its pathogenesis was obscure for many years. In 1911 Cannata⁶ postulated an adrenal insufficiency with consequent loss of vascular tone. Bauch² (1916) referred to a toxic degeneration of vascular endothelium, and Pratsicas⁷ (1924) to a cutaneous and intestinal embolism in the course of tuberculous bacillemia. The latter explanation made miliary tuberculosis a necessary precursor of the purpura.

The role of the spleen in this type of purpura was previously unknown or ignored as in the report of Pratsicas, in which the purpura in 4 patients was accompanied by gastrointestinal hemorrhage in 3, and by splenic enlargement in all, proved at autopsy to be tuberculosis of the spleen. This finding was obscured by the emphasis placed on miliary tuberculosis as the basic cause for the purpura. "Primary" tuberculosis of the spleen does not necessarily lead to purpura. The latter was noted only twice in the 50 cases collected by Winternitz.⁸ In fact, the interesting combination of splenic tuberculosis and thrombocytopenic purpura has been reported only three times,^{1, 2, 9} the diagnosis

having been made after splenectomy or at autopsy. Earlier observers were unaware of thrombocytopenia, and it is likely that many previously cited cases of purpura in tuberculosis were identical with the case reported above. No purpuric patient today would be studied without platelet counts and bleeding-time determination. These may give the only diagnostic clue, since on exceptional occasions a tuberculous spleen of clinical significance may be only slightly enlarged, and therefore not palpable. In the case reported by Weiner and Carter² the spleen weighed 237 gm and was not palpable before operation. In Kellert's¹ patient, a splenomegaly was noted, the organ weighed 1050 gm. In most cases of "primary" or "isolated" tuberculosis of the spleen, the enlargement is an outstanding physical sign.

The term "primary tuberculosis of the spleen" was introduced many years ago by Winternitz,⁵ who emphasized its limitations. However, it is useful thus to characterize a striking splenomegaly, in many cases of extraordinary size—the organ weighing as much as 3780 gm¹⁰ and filled with massive or conglomerate tuberculous caseation, the basis of symptoms and the ultimate cause of death of the patient. This is in contrast to the insignificant and incidental tuberculous splenitis without splenic enlargement sometimes encountered at autopsy in tuberculous patients.

As originally noted, the term "primary" does not signify portal of entry or even the initial site of tuberculosis. In primary tuberculosis of the spleen it is almost certain that a primary extra-splenic involvement has long since healed and a latent splenic focus has gradually assumed clinical importance. This must account for the fact that the large majority of patients so involved are adults. Primary tuberculosis of the spleen may clinically be the only discoverable tuberculous lesion. Often, it is accompanied by tuberculosis elsewhere, which, however, is nonpulmonary in at least 50 per cent of patients. In all cases the pathologist finds a miliary invasion of the liver, via portal transport, secondary to the splenic lesion. In the case reported above there was also an important genitourinary involvement, probably a concurrent development. We have pointedly ignored it, emphasizing instead the involvement of the spleen and bone marrow, which certainly was the cause of the patient's hemorrhagic tendency and finally of his death. However, in passing, it should be pointed out that recognition of the tuberculous nature of the patient's genitourinary disease would possibly have led to a similar conclusion concerning the splenomegaly.

At autopsy the osseous system showed nothing of note. In view of the microscopical finding of bone-marrow involvement, the absence of tuberculous osteitis and periostitis was striking. The occurrence of miliary tuberculosis of the bone marrow has recently been reported¹¹ but we are

unaware of such widespread involvement as noted in this case with so little bone destruction.

In fields not replaced by caseation or precaseous inflammation, the bone marrow was hyperactive. The concentration of normoblasts was notable. Polycythemia has been recorded in cases of tuberculous splenomegaly.¹⁰ Our patient at first had a moderate secondary anemia, his acute anemia in the last month of life was due to hemorrhage and toxicity and possibly to a myelophthisic factor because of marrow caseation. The absence of normal megakaryocytes was probably a toxic reaction to tuberculosis—not only to systemic infection but more so, we believe, to the local bone-marrow involvement.

This patient did not have "myelofibrosis," a myelopathy in which bone-marrow elements are replaced by fibrous tissue, with compensatory extramedullary hematopoiesis in other organs of the reticuloendothelial system. It has been emphasized that myelofibrosis, previously known as a reaction to toxemia and bone-marrow irritation of various types, may also follow systemic miliary tuberculosis.¹² The spleen may or may not be involved in the tuberculous process, and although the organ is often moderately enlarged, it is decidedly not the splenomegaly known as "primary tuberculosis of the spleen." None of the 4 patients with myelofibrosis associated with tuberculosis recently reported by Crail, Alt and Nadler¹² exhibited thrombocytopenic purpura. In contrast, our patient did not show evidence of myelofibrosis or of the accompanying widespread visceral fibrosis, which seems to constitute a chronic cellular reaction peculiar to some types of miliary tuberculous infection.

Tuberculosis of the bone marrow was almost certainly a factor in this case of thrombocytopenic purpura. To what extent it governed or influenced the purpura can only be determined by future observation of similar cases, it will be interesting to see not only what information can be gleaned by bone-marrow biopsy but also what splenectomy can offer in the presence of tuberculous myelitis. This may be a new field for streptomycin therapy.

In addition, 2 cases of "primary" tuberculosis of the spleen with purpura have been seen in the last two years in the large post-mortem experience at the office of the coroner of Philadelphia. These three patients were adult Negroes. Death resulted from gastrointestinal hemorrhage. The second case showed, as did the first, a tuberculous myelitis in the sternum and in many ribs. Unfortunately, a similar study of the bone marrow was omitted in the third case. Previously reported purpura in tuberculosis has presumably been in white patients. Our own experience indicates that colored patients with fever, splenomegaly, purpura and other hemorrhagic manifestations form a group in which tuberculosis of the spleen, thrombocytopenia and bone-

into which many polymorphonuclear leukocytes had infiltrated. The periportal tissue also showed a cellular infiltration composed of many monocytes and polymorphonuclear leukocytes, but there was no increase of fibrous tissue and no biliary-duct hyperplasia.

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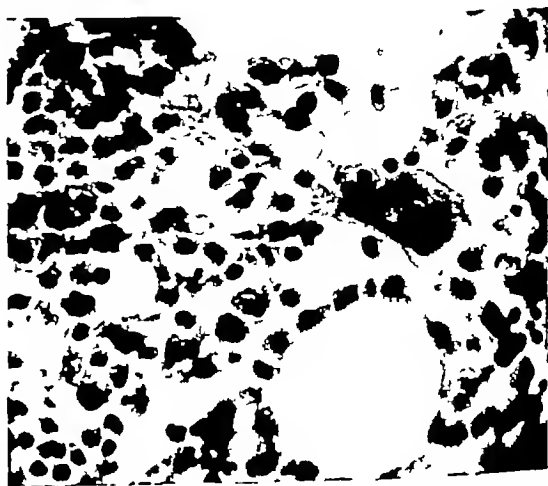


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minutes after meals. Her blood pressure was 158/80, and on vaginal examination the uterus was consistent with a 3 months' gestation. The blood serologic findings were negative, the blood was Group "A" and Rh+. Throughout this pregnancy her blood pressure varied from 150/90 to 160/90, and she complained of constant heartburn with nausea coming on while she was lying down. Urinalyses were within normal limits. On May 19, 1948 she began vomiting brownish coffee-ground material at night and noted tarry stools and weakness. She volunteered the information that the nausea and vomiting

minute Hematemesis and melena persisted, the stools being strongly positive for blood. Two 500-cc blood transfusions were given. On May 28th a gastrointestinal series (Fig 1) was interpreted as follows:

There is a single fetus of approximately 8 months in age, presenting by vertex, with the occiput to the left. There is a diaphragmatic hernia. There is no peptic ulcer or gastric carcinoma. After 5 hours there is still some barium in the bernal pouch.

On May 29 the hemoglobin was 72 per cent, and the red-cell count 3,700,000.

On the same day a vaginal cesarean section was performed under spinal anesthesia with the aid of a Schuchardt incision. A 5-pound, 8-ounce, normal living male infant was delivered from the left occipitoposterior position by rotation and extraction with Kielland forceps. The patient received a third 500-cc blood transfusion after operation and was kept in Fowler's position postoperatively. Her postoperative course was uneventful, with no heartburn or nausea, the stools becoming negative for occult blood on the 3rd postoperative day, and the highest temperature being 99.6°F. She and her infant, who then weighed 5 pounds, 12 ounces, were both discharged from the hospital in good condition on the 11th postoperative day.

When seen on July 12 the patient had no complaints. Examination disclosed a well healed perineum giving good support with no cystocele or rectocele. The cervix was clean and presented healed anterior and posterior incisions. The uterus was well involuted and normal in size, contour, position and mobility. There were no adnexal masses or tenderness. On November 8, 1949, a gastrointestinal series showed no evidence of diaphragmatic hernia.

SUMMARY

A case of strangulated diaphragmatic hernia in pregnancy with survival of mother and infant, is reported.

The literature on diaphragmatic hernia as a complication of pregnancy is briefly reviewed.

REFERENCES

1. Rigler L. G. and Eneboe J. B. Incidence of hiatus hernia in pregnant women and its significance. *J Thoracic Surg* 4:262-268 1935.
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FIGURE 1 X-ray Film Taken on May 28, Showing a Diaphragmatic Hernia of the Stomach Late in Pregnancy

bad occurred while she was lying down and had been relieved by sitting up.

On May 25 examination of the blood revealed a red-cell count of 2,600,000, with a hemoglobin of 50 per cent, and a white-cell count of 10,950 with a normal differential.

On admission to the hospital the next day the blood pressure was 130/84. The uterus rose 25 cm above the symphysis and contained a fetus estimated to be 5 lb in weight, presenting by vertex. The fetal heart sounds were clear and regular in the right lower quadrant, the rate being 130 per

marrow tuberculosis are major diagnostic possibilities

SUMMARY

A case of fatal gastrointestinal hemorrhage associated with purpura and splenic tuberculosis is reported. Tuberculosis of the bone marrow without bone destruction was noted in conjunction with abnormality of megakaryocytes.

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STRANGULATED DIAPHRAGMATIC HERNIA COMPLICATING PREGNANCY*

Report of a Case

GEORGE A. BOURGEOIS, M.D.† AND WILFRED T. HOOD, M.D.‡

MARLBOROUGH, MASSACHUSETTS

DIAPHRAGMATIC hernia is not a rare complication of pregnancy. By roentgenologic examination Rigler and Eneboe¹ demonstrated this condition in 25, or 12.8 per cent, of 195 women in the last trimester of pregnancy, in 4, or 5.1 per cent, of 71 primiparas, and in 21, or 18.1 per cent, of 116 multiparas. They reached the conclusions that diaphragmatic hernia is commoner in the female than in the male, that its incidence increases with age and repeated pregnancy and that increased intra-abdominal pressure is an important etiologic factor. Mengert and Murphy² showed that intra-abdominal pressure is increased by voluntary muscular effort during labor.

Although relatively common during pregnancy, diaphragmatic hernia is seldom responsible for major symptomatology. It is generally recognized as a cause of persistent and intractable pyrosis and other minor gastrointestinal symptoms, characteristically aggravated by the horizontal and relieved by the upright position.³ But the few cases of strangulation recorded in the literature spell a high incidence of tragedy. Maternal deaths are reported in the ante-partum period by R. O. Muller⁴ and by Keim, Rosenthal and Hugier,⁵ in the intra-partum period by Granzow⁶ and by Diddle and Tidrick,⁷ and in the post-partum period by Legry.⁸ Maternal survivals are recorded by Salgado⁹ (cesarean section early in labor), by DeLee and Gilson¹⁰ (strangulation occurring post partum and responding to conservative treatment) and by Thompson and Le-

Blanc¹¹ (intra-partum strangulation with successful post-partum operation).

In the case reported below the patient experienced pyrosis throughout the greater part of two pregnancies. During the last ten days of her second pregnancy strangulation of the diaphragmatic hernia was manifested by hematemesis and melena. The diagnosis was established by x-ray examination. Definitive management of the problem was predicated on reduction of intra-abdominal pressure by prompt evacuation of the uterus without labor, spinal block being employed as the anesthesia of choice. Evacuation of the uterus was accomplished by vaginal cesarean section because the infant was small, and an extraperitoneal procedure promised a clean peritoneal cavity if surgery directed at the diaphragmatic hernia became necessary. Fortunately, the hernia underwent spontaneous reduction after delivery.

CASE REPORT

Mrs. N. T., a 31-year-old secundigravida, had begun her last normal menstrual period on August 30, 1947, her expected date of confinement being June 6, 1948.

Except during her pregnancies the patient had always been well. She had had no serious illnesses, no operations and no injuries. The menarche had occurred at 12 years of age, and her periods had been regular, occurring about every 28 days and lasting 4 or 5 days with moderate flow and no pain. The family history was irrelevant.

The patient had delivered spontaneously at term a 3-pound, 13-ounce, male infant on November 19, 1941. Throughout this pregnancy she had complained of severe heartburn, and at times of puffiness about the hands and face. She was kept on a low-salt diet during the last 2 months of gestation. On admission to the hospital for delivery her blood pressure was 156/90, and urinalysis showed slight albuminuria. The infant survived.

The patient was first seen on November 30, 1947. She complained of heartburn and nausea occurring about 30

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‡Member active staff Marlborough Hospital; member courtesy staff Clinton Hospital, Clinton, Massachusetts.

minutes after meals. Her blood pressure was 158/80, and on vaginal examination the uterus was consistent with a 3 months' gestation. The blood serologic findings were negative, the blood was Group "A" and Rh+. Throughout this pregnancy her blood pressure varied from 150/90 to 160/90, and she complained of constant heartburn with nausea coming on while she was lying down. Urinalyses were within normal limits. On May 19, 1948, she began vomiting brownish coffee-ground material at night and noted tarry stools and weakness. She volunteered the information that the nausea and vomiting

minute. Hematemesis and melena persisted, the stools being strongly positive for blood. Two 500-cc blood transfusions were given. On May 28th a gastrointestinal series (Fig. 1) was interpreted as follows:

There is a single fetus of approximately 8 months in age, presenting by vertex, with the occiput to the left. There is a diaphragmatic hernia. There is no peptic ulcer or gastric carcinoma. After 5 hours there is still some barium in the hernial pouch.

On May 29 the hemoglobin was 72 per cent, and the red-cell count 700,000.

On the same day a vaginal cesarean section was performed under spinal anesthesia with the aid of a Schuchardt incision. A 6-pound, 8-ounce, normal living male infant was delivered from the left occipitoposterior position by rotation and extraction with Kielland forceps. The patient received a third 500-cc blood transfusion after operation and was kept in Fowler's position postoperatively. Her postoperative course was uneventful, with no heartburn or nausea, the stools becoming negative for occult blood on the 3rd postoperative day and the highest temperature being 99.6°F. She and her infant, who then weighed 5 pounds, 12 ounces, were both discharged from the hospital in good condition on the 11th postoperative day.

When seen on July 12 the patient had no complaints. Examination disclosed a well healed perineum giving good support with no cystocele or rectocele. The cervix was clean and presented healed anterior and posterior incisions. The uterus was well involuted and normal in size, contour, position and mobility. There were no adnexal masses or tenderness. On November 8, 1949, a gastrointestinal series showed no evidence of diaphragmatic hernia.

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MEDICAL PROGRESS

ENDOSCOPY*

EDWARD B. BENEDICT, M D †

BOSTON

PROGRESS in endoscopy during the past two years has been marked by an improvement in diagnostic methods. These, in turn, have been aided by the use of new instruments. It seems fitting that this article should be devoted to a survey of the technical advances and to a re-emphasis of some of the important aspects of endoscopy.

BRONCHOSCOPY

This is such a well established procedure in the diagnosis and treatment of bronchopulmonary disease that one might think there would be little that was new to report. However, improved technic by the use of the Broyles‡ broncho-

cancer-cell study (Papanicolaou¹) By the use of this method Gibbon et al² report a very high incidence of positive results in carcinomas inaccessible to direct visualization by bronchoscopy, and negative to cancer-cell sputum study. Their results are reviewed in Table 1 and 2.

My own experience in a study of 309 proved cases of primary bronchogenic carcinoma reveals that bronchoscopic biopsy was positive in 189 cases (61 per cent), and that in 5 additional cases cancer cells were found in the secretions aspirated at the time of bronchoscopy. With improved technic in washing out of the bronchus leading to the area under suspicion, cancer cells may be found more frequently.

At the risk of repetition and at the risk of pointing out what to many is obvious, I emphasize again the indications for bronchoscopy. This procedure is of real assistance in establishing a diagnosis when symptoms exist such as cough, hemoptysis and wheeze. Unfortunately, this diagnostic aid is not always used when indicated. Furthermore bronchoscopy should be performed in cases of bronchial obstruction, atelectasis, tuberculosis, lung abscess, bronchiectasis, tumor and foreign body.

The importance of bronchoscopy in hemoptysis when x-ray examination may be negative or inconclusive should be particularly emphasized. In a recent case in which hemoptysis was the presenting

TABLE 1 *Bronchoscopic Diagnosis in 118 Cases of Carcinoma of the Lung*

DIAGNOSIS	NO OF CASES	PERCENTAGE
Positive biopsy	52	44
Other suggestive bronchoscopic evidence	23	20
Neoplastic cells found	105	89
Neoplastic cells found bronchoscopy completely negative	43	36

scope makes the introduction of the instrument easier for the patient and the visibility better for the bronchoscopist. The Broyles bronchoscope, having an expanded lumen proximally, permits the operator to visualize the vocal cords very easily without the aid of the cumbersome laryngoscope, and the patient is subjected to less discomfort when the bronchoscope is introduced into the trachea. The visibility is further increased by improved lighting and by the use of foroblique, right-angle and retrograde telescopes for inspection of the various bronchial orifices that are beyond the reach of the straight bronchoscope. Biopsies may be taken in the usual manner or with special forceps provided for use in conjunction with the foroblique telescope. Tumors or stenoses of the upper-lobe orifices, invisible by direct bronchoscopy, may be readily visualized by the use of the right-angle telescope.

Another major advance in bronchoscopic technic is the special method of aspirating secretions for

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†Clinical associate in surgery, Harvard Medical School; endoscopist, Massachusetts General Hospital.

‡Designed by Dr. Edwin A. Broyles, of the Johns Hopkins Hospital and manufactured by the American Cystoscope Makers, Incorporated, New York City.

TABLE 2 *Bronchoscopic Diagnosis in 31 Patients Explored*

DIAGNOSIS	NO OF CASES	PERCENTAGE
Positive biopsy	18	58
Neoplastic cells but no biopsy	9	29
No neoplastic cells and no biopsy	4	13

symptom x-ray films were taken on several occasions and were said to be essentially normal or to show some bronchiectasis. Everybody seemed satisfied and bronchoscopy was not suggested by any of three physicians until nine months had elapsed. At the time of bronchoscopy a carcinoma of the right main bronchus was easily demonstrated, and biopsy obtained. Fortunately, the lesion appeared to be favorable for pneumonectomy which was successfully carried out a few days later. Since several similar cases have come to my attention

recently, I consider it of the greatest importance to stress the value of bronchoscopy in hemioptysis

ESOPHAGOSCOPY

In this field of endoscopy, the most important point to emphasize is one that is by no means new but is far too often neglected by the medical profession. Reference is made to the use of a previously swallowed thread as a guide to bougienage and sometimes as a guide to esophagoscopy. As long as a patient can swallow water, he can swallow a thread (No 1 white silk), and thus keep a lumen open. If the lumen is not kept open it all too often shuts down very suddenly and completely. Such a complete stoppage frequently occurs when least expected, many weeks after live ingestion or during or after radiation therapy for carcinoma. Just prior to complete stoppage the physician in charge, and also the patient, may be lulled into a false sense of security by the latter's ability to take liquids or even very soft solids. The esophagoscopist, as well as the patient, is very much "up against it" when there is absolutely no lumen whatever and no thread to guide the way. It is admitted that occasionally a lumen can be re-established by very gentle probing with a small bougie used under direct vision through the esophagoscope, and also that intravenous therapy with improved hydration sometimes results in a spontaneous reopening of a lumen, but the wise physician should never wait for this eventuality. Therefore in the early stages of a live stricture or preliminary to radiation therapy for carcinoma of the esophagus, he should *instruct the patient to swallow a continuous No 1 white silk thread*, at the rate of about 15 cm per hour, keeping the spool in his breast pocket, and cutting off the distal end as it appears at the anus, and, secondly, he should *call in a competent esophagologist*.

Another point worth emphasizing is that in a patient suspected of having carcinoma of the esophagus, one negative biopsy does not exclude it. At least one more biopsy should be obtained from deep within the lumen of the narrowed area.

GASTROSCOPY

The development of the Benedict operating gastroscope** has opened a new field for positive gastroscopic diagnosis. With this instrument it is possible to aspirate secretions (and thus to permit better visualization of the stomach) and to obtain biopsies for accurate microscopical diagnosis. This instrument was first used in March, 1948, and since then 50 biopsies have been obtained with the positive microscopical diagnoses listed in Table 3. There have been no accidents or complications.

One of the most valuable uses of gastroscopic biopsy is in the diagnosis of lymphoma. From the gross appearance alone when viewed through the

gastroscope, lymphoma is readily mistaken for gastritis or diffuse infiltrating carcinoma. Therefore, the obtaining of a biopsy is of very great importance. A positive biopsy is more valuable than a negative biopsy, but when one is dealing with a diffuse process a negative biopsy, adequately taken from a representative area, should go a long way toward excluding lymphoma. A positive biopsy definitely clinches an otherwise impossible diagnosis.

In the diagnosis of carcinoma of the stomach, when doubt exists from the clinical, laboratory and x-ray standpoint, a positive gastroscopic biopsy

TABLE 3 Microscopical Diagnoses of Specimens Obtained with Benedict Operating Gastroscope

DIAGNOSIS	NO OF CASES
Gastritis (all types and degrees)	24
Normal stomach	13
Inadequate specimen	6
Carcinoma	2
Carcinoma or lymphoma (later proved to be lymphoma)	1
Lymphoma	1
Cystic dilatation and edema	1
Total	50

is of great importance. A negative biopsy does not exclude carcinoma.

In spite of the great increase in knowledge of gastritis since the development of the Wolf-Schindler,⁴ flexible gastroscope, the surface has barely been scratched in attempts to correlate the clinical, radiologic, gastroscopic and pathological findings in gastritis.^{5, 6} From the 50 biopsies already taken and studied by Dr Tracy B Mallory and me, it is apparent that much remains to be done in determining the limits of normal gastric histology, and in classifying the type and severity of gastritis. It is probable that postoperative gastritis does not exist as a separate entity. Thick folds do not necessarily mean gastritis. Reddening, edema and adherent secretion may be present in a gastric mucosa that shows no significant histologic change. On the other hand, there may be pathological evidence of gastritis in a stomach that looks normal to the endoscopist.

This relatively easy method of gastric biopsy is thus already of clinical importance and will eventually lead to a better understanding of gastric histopathology.

PERITONEOSCOPY

In this field of endoscopy no new instruments have been developed, but I wish to emphasize the increasing value of the procedure, which permits positive diagnosis of carcinoma of the liver, carcinomatosis, tuberculous peritonitis, abdominal and pelvic tumors, unexplained ascites and so forth without laparotomy. In many cases it saves unnecessary exploratory laparotomy. Furthermore, it can be safely performed on patients who are too

*Manufactured by the American Cystoscope Makers Incorporated New York City

sick to justify major surgical procedures, but in whom it is important to obtain a positive diagnosis. Biopsy specimens can and should be obtained in almost all cases.

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MASSACHUSETTS MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND SIXTY-EIGHTH ANNIVERSARY

May 24, 25 and 26, 1949

THE one hundred and sixty-eighth anniversary of the Massachusetts Medical Society was observed at the Worcester Memorial Auditorium in Worcester on May 24, 25 and 26, 1949.

Twelve hundred and thirty physicians, 224 exors and 100 ladies were registered. The Supervising Censors met in Room E at the Hotel Sheraton on May 23 at 4 30 p m. This meeting was followed by the Cotting Supper in the Ballroom of the Hotel Sheraton, which was attended by 207 councilors. The annual meeting of the Council followed this supper at 7 00 p m, with 203 councilors in attendance, as recorded in the attendance books.

TUESDAY, MAY 24

The first general session opened at 9 00 a m in the Little Theater of the Auditorium under the co-chairmanship of Dr John J Dumphy and Dr Bancroft C Wheeler.

The one hundred and sixty-eighth annual meeting of the Society was held in the Little Theater at 11 00 a m. President Daniel B Reardon presided. The attendance was about 150. Dr Reardon spoke on "The State of the Society," after which the annual oration, "Some Responsibilities of Medical Education," was delivered by Dr C Sidney Burwell. (This lecture appeared in the June 9 issue of the *Journal*.) The annual luncheon was served on the stage of the Auditorium to 135 fellows.

The second general session was held in the Little Theater at 2 00 p m under the co-chairmanship of Dr Edward P Bagg and Dr Donald Munro.

WEDNESDAY, MAY 25

The third general session was held at 9 00 a m under the co-chairmanship of Dr George R Dunlop and Dr Fred H Allen. The Shattuck Lecture was delivered at 11 05 a m by Dr Paul D White, of Boston, on the subject, "La Médecine du Cœur." (This lecture appeared in the May 26 issue of the *Journal*.)

At noon certain of the sections held their luncheons, followed by their annual meetings. The Section of Medicine, under the chairmanship of Dr Laurence B Ellis, met on the stage. The attendance was 89. The Section on Pediatrics met in the Assembly Room under the chairmanship of Dr W Bradford Adams. The attendance was 48. The Section on Radiology, under the chairmanship of Dr Albert M Moloney, met in the Male Chorus Room with 40 in attendance. The Section on Physical Medicine met in the Musicians' Room, under the chairmanship of Dr David C Dittmore, with 38 in attendance.

At 2 00 p m the fourth general session was held in the Little Theater under the co-chairmanship of Dr Donald B Cheetham and Dr Lawrence R Dame.

The annual dinner was held in the Ballroom of the Hotel Sheraton at 7 00 p m with 439 in attendance. The speaker of the evening was Roscoe Pound, LL D, University Professor Emeritus of Harvard University and former dean of Harvard Law School, who delivered an address entitled, "The Professions in the Society of Today."

THURSDAY, MAY 26

The fifth general session was held in the Little Theater at 9 00 a m under the joint chairmanship of Dr James T Brosnan and Dr Norman B McWilliams.

At noon the remaining scientific sections held their luncheons and meetings. The Section of Surgery met on the stage under the chairmanship of Dr Robert E Gross, with 27 in attendance. The Section of Obstetrics and Gynecology met in the Male Chorus Room, under the chairmanship of Dr James F Conway, with 40 in attendance. The Section of Dermatology and Syphilology, under the chairmanship of Dr Francis P McCarthy, met in the Female Chorus Room with 30 in attendance. The Section of Anesthesiology met in the Assembly Room, under the chairmanship of Dr Morris J Nicholson, with 40 in attendance, and the Section

on Physiology and Pathology, under the chairmanship of Dr Monroe J Schlesinger met in the Musicians' Room with 37 in attendance

The sixth general session was held at 2:00 p m under the co-chairmanship of Dr George L Schadt and Dr John F Casey

An exhibition of works of art by members of the Massachusetts Physicians' Art Association was on view throughout the meeting

The special list of officers, standing and special committees councilors censors admissions and deaths is appended

H QUIMBY GALLUPE, *Secretary*

ANNUAL MEETING OF THE SOCIETY

The one hundred and sixty-eighth annual meeting of the Massachusetts Medical Society was called to order by the president, Dr Daniel B Reardon, in the Little Theater of the Memorial Auditorium in Worcester at 11:00 a m on May 24

Dr Reardon introduced Dr John J Dumphy, the retiring president of the Worcester District Medical Society, who spoke as follows

Worcester is very happy to welcome the meeting of the Massachusetts Medical Society for the third time in one hundred and sixty-eight years. We are glad to have you see our medical facilities, our library and our city. We have had our local committee working in co-operation with the state committee for many months to make this meeting a success. We hope you will enjoy yourselves.

The President then introduced the honorable Charles F Jeff Sullivan, lieutenant governor of the Commonwealth, and mayor of the City of Worcester, who addressed the meeting as follows

It is indeed a real privilege and a pleasure to extend official and personal greetings on the occasion of your one hundred and sixty-eighth annual meeting.

Worcester, its citizens and I as its mayor, and Massachusetts and I as its lieutenant governor, are honored at the selection of the heart of the Commonwealth for the annual conferences and sessions of the Massachusetts Medical Society. And in behalf of all of the citizens, I bid you a hearty welcome. Worcester and the Commonwealth are proud of the national and international distinction and reputation of our physicians. They are proud that our physicians have achieved in the noble profession of medicine the advancement of medical science, brought comfort to the afflicted, prolonged life expectancy and turned despair into confidence and hope.

In the prevention and cure of disease that ravages the body and mind of man, remarkable progress has been made. Study and research continue without abatement to relieve suffering humanity. Your intense unselfish efforts are to be commended and encouraged. You of the medical profession have a glorious tradition of centuries, a heritage that must be preserved and enhanced.

Worcester and Massachusetts salute you, the members of the Massachusetts Medical Society, and are grateful for your individual and collective service to your fellow men.

We bid you godspeed in your constant efforts in searching out the cause, prevention and cure of disease that bring worry and misery to the human race. Your destiny and your duty you have always recognized, and you have proved faithful to your sacred trust.

I know that, true to your profound oath, you will carry on in the highest, noblest tradition of your chosen profession.

The Secretary submitted the record of the 1948 annual meeting, held on May 25, 1948, as published in the July 29, 1948, issue of the *New England Journal of Medicine*, and moved its acceptance. The motion was seconded and so voted.

The President then called upon Dr Edward P Bagg, chairman of the Committee on By-laws and Council Rules, who addressed the meeting as follows

The Secretary informs me that the printed copies of the proposed changes in the by-laws have been distributed. I should like to offer some final corrections, as they were approved last night at the Council meeting.

On the first page, the resolution regarding Chapter IV, Section 3, is corrected by the substitution of the word "to" for the word "under," and the insertion of the word "on" before the word "by-laws."

Likewise, later in the same chapter, the words "to the" should be substituted for "under."

Otherwise, the copy as printed in the circular is correct. The corrections have already been approved by the Council. I move that the proposed changes in the by-laws be adopted by the Society.

The motion was seconded, and it was so voted.

The Secretary reported on the membership of the Society as follows

The membership in May, 1948, was 6538. This has increased by 304 new members admitted since then, in addition to 6 re-instatements, bringing it to a total of 6848. Losses were 6 by deprivations, 30 by resignation and about 60 by death, which brings the sum total to 6752 members as of May 24, 1949.

A motion to approve the report was offered and seconded, and it was so voted.

At the request of the President, the vice-president, Dr Donald Munro, assumed the chair and Dr Reardon gave the following address

Again, as for many generations past, the Society meets to review the accomplishments of another year. I venture to state that never in our long and eventful history have we passed such a period as the last twelve months. For today our task is not the simple one of progress in the field of medicine. Rather, it is the hutching of a professional fortress against what has seemed to us to be the attack of our own government. Never in the memories of those of us long in practice have the conditions obtained that have confronted us during the tenure of office of those who now yield up their duties to the hands of the incoming officers. I like to believe that we have met this challenge in our time. I know that we have done our best not to fail the thousands of our fellows who have placed their cause in our hands. I speak the gratitude of all of us to our permanent officers, who in their help and guidance have made this year one of which the Society may well be proud.

A brief recital of achievement is due to you. Thus, I should like to review the work of several of our departments in particular that you may realize that the torch has been borne by willing hands for all.

The Committee on Public Relations has been active as usual. Public relations was stimulated this year by the incorporation of the Massachusetts Health Conference, the first meeting of which was held at the Hotel Statler, Boston, on February 19 and 20, when about 1000 people, both lay and professional, participated. This conference was the result of activity by the chairman of the Massachusetts Medical Society Committee on Public Relations who stepped down from the chairmanship and formed a conference of which Dr John F Conlin was elected president. As Dr Conlin stated "At no time previously has there been a mass, concentrated attempt here to bring consumers and distributors of health services—

sick to justify major surgical procedures, but in whom it is important to obtain a positive diagnosis. Biopsy specimens can and should be obtained in almost all cases.

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- 5 Benedict, E B and Mallory T B. *Correlation of gastroscopic and pathological findings in gastritis*. *Surg., Gynec. & Obst.* 76:129-135, 1943.
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MASSACHUSETTS MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND SIXTY-EIGHTH ANNIVERSARY

May 24, 25 and 26, 1949

THE one hundred and sixty-eighth anniversary of the Massachusetts Medical Society was observed at the Worcester Memorial Auditorium in Worcester on May 24, 25 and 26, 1949.

Twelve hundred and thirty physicians, 224 exors and 100 ladies were registered.

The Supervising Censors met in Room E at the Hotel Sheraton on May 23 at 4:30 p.m. This meeting was followed by the Cotting Supper in the Ballroom of the Hotel Sheraton, which was attended by 207 councilors. The annual meeting of the Council followed this supper at 7:00 p.m., with 203 councilors in attendance, as recorded in the attendance books.

TUESDAY, MAY 24

The first general session opened at 9:00 a.m. in the Little Theater of the Auditorium under the co-chairmanship of Dr. John J. Dumphy and Dr. Bancroft C. Wheeler.

The one hundred and sixty-eighth annual meeting of the Society was held in the Little Theater at 11:00 a.m. President Daniel B. Reardon presided. The attendance was about 150. Dr. Reardon spoke on "The State of the Society," after which the annual oration, "Some Responsibilities of Medical Education," was delivered by Dr. C. Sidney Burwell. (This lecture appeared in the June 9 issue of the *Journal*.) The annual luncheon was served on the stage of the Auditorium to 135 fellows.

The second general session was held in the Little Theater at 2:00 p.m. under the co-chairmanship of Dr. Edward P. Bagg and Dr. Donald Munro.

WEDNESDAY, MAY 25

The third general session was held at 9:00 a.m. under the co-chairmanship of Dr. George R. Dunlop and Dr. Fred H. Allen. The Shattuck Lecture was delivered at 11:05 a.m. by Dr. Paul D. White, of Boston, on the subject, "La Médecine du Coeur" (This lecture appeared in the May 26 issue of the *Journal*.)

At noon certain of the sections held their luncheons, followed by their annual meetings. The Section of Medicine, under the chairmanship of Dr. Laurence B. Ellis, met on the stage. The attendance was 89. The Section on Pediatrics met in the Assembly Room under the chairmanship of Dr. W. Bradford Adams. The attendance was 48. The Section on Radiology, under the chairmanship of Dr. Albert M. Moloney, met in the Male Chorus Room with 40 in attendance. The Section on Physical Medicine met in the Musicians' Room, under the chairmanship of Dr. David C. Ditmore, with 38 in attendance.

At 2:00 p.m. the fourth general session was held in the Little Theater under the co-chairmanship of Dr. Donald B. Cheetham and Dr. Lawrence R. Dame.

The annual dinner was held in the Ballroom of the Hotel Sheraton at 7:00 p.m. with 439 in attendance. The speaker of the evening was Roscoe Pound, LL.D., University Professor Emeritus of Harvard University and former dean of Harvard Law School, who delivered an address entitled, "The Professions in the Society of Today."

THURSDAY, MAY 26

The fifth general session was held in the Little Theater at 9:00 a.m. under the joint chairmanship of Dr. James T. Brosnan and Dr. Norman B. McWilliams.

At noon the remaining scientific sections held their luncheons and meetings. The Section of Surgery met on the stage under the chairmanship of Dr. Robert E. Gross, with 27 in attendance. The Section of Obstetrics and Gynecology met in the Male Chorus Room, under the chairmanship of Dr. James F. Conway, with 40 in attendance. The Section of Dermatology and Syphilology, under the chairmanship of Dr. Francis P. McCarthy, met in the Female Chorus Room with 30 in attendance. The Section of Anesthesiology met in the Assembly Room, under the chairmanship of Dr. Morris J. Nicholson, with 40 in attendance, and the Section

on Physiology and Pathology, under the chairmanship of Dr Monroe J Schlesinger, met in the Musicians' Room with 37 in attendance

The sixth general session was held at 2 00 p m under the co-chairmanship of Dr George L Schadt and Dr John F Casey

An exhibition of works of art by members of the Massachusetts Physicians' Art Association was on view throughout the meeting

The special list of officers, standing and special committees, councilors, censors, admissions and deaths is appended

H QUIMBY GALLUPE, *Secretary*

ANNUAL MEETING OF THE SOCIETY

The one hundred and sixty-eighth annual meeting of the Massachusetts Medical Society was called to order by the president, Dr Daniel B Reardon, in the Little Theater of the Memorial Auditorium in Worcester at 11 00 a m on May 24

Dr Reardon introduced Dr John J Dumphy, the retiring president of the Worcester District Medical Society, who spoke as follows

Worcester is very happy to welcome the meeting of the Massachusetts Medical Society for the third time in one hundred and sixty-eight years We are glad to have you see our medical facilities, our library and our city We have had our local committee working in co-operation with the state committee for many months to make this meeting a success We hope you will enjoy yourselves

The President then introduced the honorable Charles F Jeff Sullivan, lieutenant governor of the Commonwealth, and mayor of the City of Worcester, who addressed the meeting as follows

It is indeed a real privilege and a pleasure to extend official and personal greetings on the occasion of your one hundred and sixty-eighth annual meeting

Worcester, its citizens and I as its mayor, and Massachusetts, and I as its lieutenant governor, are honored at the selection of the heart of the Commonwealth for the annual conferences and sessions of the Massachusetts Medical Society And in behalf of all of the citizens, I bid you a hearty welcome Worcester and the Commonwealth are proud of the national and international distinction and reputation of our physicians They are proud that our physicians have achieved in the noble profession of medicine the advancement of medical science, brought comfort to the afflicted, prolonged life expectancy and turned despair into confidence and hope

In the prevention and cure of disease that ravages the body and mind of man, remarkable progress has been made Study and research continue without abatement to relieve suffering humanity Your intense unselfish efforts are to be commended and encouraged You of the medical profession have a glorious tradition of centuries, a heritage that must be preserved and enhanced

Worcester and Massachusetts salute you, the members of the Massachusetts Medical Society, and are grateful for your individual and collective service to your fellow men

We bid you godspeed in your constant efforts in searching out the cause, prevention and cure of disease that bring worry and misery to the human race Your destiny and your duty you have always recognized, and you have proved faithful to your sacred trust

I know that, true to your profound oath, you will carry on in the highest, noblest tradition of your chosen profession

The Secretary submitted the record of the 1948 annual meeting, held on May 25, 1948, as published in the July 29, 1948, issue of the *New England Journal of Medicine*, and moved its acceptance The motion was seconded and so voted

The President then called upon Dr Edward P Bagg, chairman of the Committee on By-laws and Council Rules, who addressed the meeting as follows

The Secretary informs me that the printed copies of the proposed changes in the by-laws have been distributed I should like to offer some final corrections, as they were approved last night at the Council meeting

On the first page, the resolution regarding Chapter IV, Section 3, is corrected by the substitution of the word "to" for the word "under," and the insertion of the word "on" before the word "by-laws"

Likewise, later in the same chapter, the words "to the" should be substituted for "under"

Otherwise, the copy as printed in the circular is correct. The corrections have already been approved by the Council I move that the proposed changes in the by-laws be adopted by the Society

The motion was seconded, and it was so voted

The Secretary reported on the membership of the Society as follows

The membership in May, 1948, was 6538 This has increased by 304 new members admitted since then, in addition to 6 re-instatements, bringing it to a total of 6848 Losses were 6 by deprivations 30 by resignation and about 60 by death, which brings the sum total to 6752 members as of May 24 1949

A motion to approve the report was offered and seconded, and it was so voted

At the request of the President, the vice-president, Dr Donald Munro, assumed the chair and Dr Reardon gave the following address

Again, as for many generations past, the Society meets to review the accomplishments of another year I venture to state that never in our long and eventful history have we passed such a period as the last twelve months For today our task is not the simple one of progress in the field of medicine Rather, it is the buttressing of a professional fortress against what has seemed to us to be the attack of our own government Never in the memories of those of us long in practice have the conditions obtained that have confronted us during the tenure of office of those who now yield up their duties to the hands of the incoming officers I like to believe that we have met this challenge in our time I know that we have done our best not to fail the thousands of our fellows who have placed their cause in our hands I speak the gratitude of all of us to our permanent officers, who in their help and guidance have made this year one of which the Society may well be proud

A brief recital of achievement is due to you Thus, I should like to review the work of several of our departments in particular that you may realize that the torch has been borne by willing hands for all

The Committee on Public Relations has been active as usual Public relations was stimulated this year by the incorporation of the Massachusetts Health Conference, the first meeting of which was held at the Hotel Statler, Boston, on February 19 and 20, when about 1000 people, both lay and professional, participated This conference was the result of activity by the chairman of the Massachusetts Medical Society Committee on Public Relations who stepped down from the chairmanship and formed a conference of which Dr John F Conlin was elected president As Dr Conlin stated "At no time previously has there been a mass, concentrated attempt here to bring consumers and distributors of health services —

the people who are receiving and the people who are doing—together for an exchange of information. Its success was indicated by the conference's unanimous vote to continue with a similar session a year hence." The reaction to this conference was widespread, and many states have written asking for details. We believe this to have been a step in the right direction of good public relations.

The great work of the *New England Journal of Medicine* has gone forward with ever-increasing success. We are fortunate in Dr. Joseph Garland. Scholarly and able, he maintains the circulation at its highest point in history. Well over 6000 copies go to the fellows of the Society in good standing. Fourteen thousand others go to regular paid subscribers all over the world. Over 4000 additional subscriptions go to students who will follow us. Nearly 500 more go to the entire membership of the New Hampshire Medical Society, and exchanges are in effect with 185 other medical journals, all of which go to the Boston Medical Library. The operation of this enterprise is marked by very real leadership and vision, and the *Journal* is a major factor among the influences that make the Commonwealth the medical center that it is. We rejoice in its continuing success and applaud the men who make that success possible.

This meeting marks the end of the first full year of our new permanent secretary. His task has been primarily to correlate work of the various committees of the Society to the end that conflicts in meetings may be eliminated, to see to it that developments in the national and state picture are made available to district societies and to conduct the office in Boston so that it functions at maximum efficiency with a greatly increased load. Deadlines have been established for committee reports, that the Council might have all matters pertinent to its deliberations in its hands in proper shape by meeting day. Co-ordination between the secretaries of the various district societies has been heightened by their gathering together for the discussion of mutual plans and problems. A new directory of fellows and a new edition of the by-laws are in process of publication. Office routine has been improved by the introduction of modern office methods and machines to cope with the added tasks presented by our growing membership. The attention to duty and the initiative exhibited by the Secretary should command the respect that is due him for his efforts over these last months. In departing my office I am most happy to know that my successors have no reason for worry whatsoever in the splendid work of Quimby Gallupe.

And what a performance the Director of Medical Education has turned in! I state it as a fact that we owe him a debt that unfortunately many, many of our members will never appreciate. Tireless, fearless, he has carried the story that must be told to every corner of the Commonwealth. Speaking seven days a week, often three and four times a day in widely separated localities in Massachusetts, he has fought the fight that is ours. In the service clubs, before Chambers of Commerce, on Beacon Hill, he has striven to repair our relations with the public. That they were in sad need of such repair no one can doubt. That we have the man for the job is susceptible to even less doubt. I say that John Conlin has been a task force all by himself that only those who have watched his work closely can truly appreciate. It will be a sad day for the Society if he ever leaves us. I commend him publicly as he should be commended. No man in my memory has done more for us.

Our work has carried us forward in other fields. Again this year as before we have sponsored the Postgraduate Assembly at Sanders College, so-called. We have been able thereby to bring to busy practitioners the renovation of methods and techniques that keeps the doctor abreast of the rapid progress in his field. The attendance has been exceptionally good, the results are felt in every town where our students care for patients. It is a highly laudable work, and those who plan for and govern its program, most particularly Richard Ohler, contribute to the community the share that is worthy of the true physician. The assemblies are ever better, and the enterprise now well established by us will continue.

The Treasurer's report is available to you, and a quick review should convince you that we are reasonably pros-

perous, as indeed we should be. The loyalty of our fellows in financial matters is traditional with us, and I am glad to testify to its continuance.

The work of all our numerous committees has progressed apace. The members have been faithful, and tribute is due also to them, for on our sustaining committees depends in large measure our ability to function as we should.

We have been materially assisted in recent months by the continued growth of our woman's auxiliary. There are twelve district auxiliaries now functioning with an organization totaling over 1000 wives of physicians. It is hoped to complete the organization of auxiliary societies in every district by the fall. There is much that has already been done by the ladies, and there is very much more that can be done particularly in the field of work in the secondary schools leading to the choice of medicine and nursing by the students as a career. The help thus rendered us can be invaluable in many spheres in the future.

I wish to emphasize one forward step that has been taken this year relative to our headquarters. In October, 1948, I was in receipt of a communication from Ludlow Griscom, a moving force in the plans for the Museum of Science that is to be constructed in Boston on the 6 acres located at the base of the Charles River basin. He suggested the possibility of the Society's taking over a wing in the new building, which is to be a substantial one. As a result, at my request, the Committee on Society Headquarters has held a number of helpful conferences with the trustees in charge of the project, and it is not beyond the realm of possibility that out of these exploratory meetings may come a solution of the problem of space that has plagued us for some time. I urge upon the Council and our successors a thorough examination of this matter in which may lie for us a very satisfactory answer to our need for a better home.

I desire also to refer to our participation in the growing work of the Blue Cross and Blue Shield. With the devotion to his job that seems to me to characterize so many of our workers, Dr. James C. McCann, president of the Massachusetts Medical Service, has helped provide the physician's answer to those who would engulf us. While Blue Cross ran into serious financial difficulties some time back, which resulted in the transfer of a number of Blue Cross-Blue Shield Groups to commercial coverage unfortunately obstructing enrollment activities of both corporations, the present outlook is once again favorable, and it is anticipated that a steady increase in growth is now well under way. Dr. Charles G. Hayden, executive director of the Medical Service, has recently emphasized to me two significant amendments in the Blue Shield by-laws voted at the last meeting of the members of Blue Shield to the effect that the president of Blue Shield shall be a physician and that the Board of Directors shall consist of from 15 to 21 members. The first amendment was a precautionary measure, whereas the second permits the introduction of younger physicians into the Blue Shield Board of Directors that there may always be continuity of medical experience and guidance. Also, changes have recently been made in the type of contracts afforded the public, with the thought that the broader coverage offered will provide an answer to some of the objections to the older type of contract that have been voiced from time to time. The growth of our voluntary health plans is a necessity for us in these days, and, therefore, I am happy to report to you the progress in both organizations which I have just mentioned.

There are just a few thoughts that, as your retiring president, I should like to leave with you. It is first of all impossible for me to thank by name all those whom I should like to mention. Time does not permit that I do so, and many of the more retiring of our collaborators do their work quietly and without general acclaim. That is as they wish it, and I respect their wishes. One cannot serve a year in the position that I have occupied without acquiring a rather definite philosophy on matters that involve us. I admit that my own feelings are colored by my own forty-six years as a physician. However that may be, bear with me a moment longer, and let us test our position in the life of the Commonwealth. I claim

that we have a real fight on our hands and that we need fighters to engage in the battle. Somewhere along the line our morale has slipped a bit. Our men, and in particular our younger men, must realize that if we have battled a bit more on some of these national programs than they like the long view indicates that we have battled for them. I referred earlier to the poor public relations of the doctor. Can there be any doubt that our doctors in a sense are farther from the people than they were thirty and forty years ago? The advances in the science that is our mistress are awe inspiring to those of us trained at the turn of the century, but the practice, infinitely more skilled now than then, seems colder, more dollar minded and somewhat less sympathetic, and the people know it. That they know it constitutes our great problem. True it is that organized medicine so-called has made its mistakes, but the safeguards offered the public in our organizations far transcend in importance the mistakes that we have made. Now if it be, as I believe it is, that societies such as ours have an obligation to the public greater than what we owe ourselves, it follows that our actions should be those of a society and not of individuals. But that I do not mean that we should endeavor to place limitations on the right of individual fellows to express their thoughts on public matters that are also medical matters. I do mean, however, that individuals so expressing themselves should have in their turn a due respect for the opinions of other physicians as expressed through the medical societies. To create by individual public statement a belief in the public mind that substantially greater division exists among doctors on the Administration's program regarding us as embodied in the bill now pending in Congress than actually exists is to do great disservice to the Society and others like it, to the profession and to the people themselves. In the course of my term, I have traveled to many of the district-society meetings throughout the Commonwealth, I have talked to individual physicians by the score, and I have seen this council, which one would ordinarily consider the proper forum on debate of matters medical, unanimously approve the fight that we are making in conjunction with other state societies against the socialization of medical practice. I have witnessed the response in our own society to the much debated assessment. Thus, I think I know as well as anyone present the sentiments held by our Massachusetts medical men on these questions. In consideration of that knowledge I judge that we have a right of protest when the policies of the Society are described in terms that would make of them minority policies in the people's mind.

One further word that I would say is this: if in our years of existence we have progressed on broad lines as a Society it has been so because of the interest of our members in our aims and objectives. I suggest it as a personal responsibility of our fellows that they pay close attention to what is going on and that they take upon themselves a larger share of the work of the Society, of which there is enough available, I can assure you. The officers at headquarters are not in essence a nest of empire builders. As I have seen, they are the group of men charged with the representation of the Society before the public and with the delivery to the Society of the type of service to which our members are entitled. The size of our membership requires large delegations of authority for speedy and efficient action, but we remain as democratic as in the earlier days. We shall continue so conditional only on the maintenance of the high level of interest by the membership. You may rest assured that your officers will look always to you for advice and counsel. In particular to you younger members do I wish to underscore the remarks that I have just made.

So it is that I end my service to you. When I entered upon the office of president a year ago I pledged you that I would do my utmost to so conduct my term that I might turn over the affairs of the Society to my successor in a condition that was just a bit improved over that which existed when I took over. I have spared no effort in that regard. It is, gentlemen, a great honor to have served in an office graced by the names that have preceded mine for a hundred and sixty-seven years. I trust you believe I have not failed you. To you all I give my thanks at this end of a most eventful year.

The President resumed the chair and asked the Secretary to show slides of the proposed location of the Boston Museum of Science on the Charles River at the dam.

The Secretary presented the slides, with a description of the location and the buildings, one of which might be the new home of the Society, the *New England Journal of Medicine* and the Boston Medical Library. The whole project was being considered by the Committee on Society Headquarters and would be presented more specifically at a future meeting of the Council of the Society.

The President then requested the Secretary to read the list of fellows who joined the Society in 1899 and were still active, and asked those present to come forward and receive a gold pin as a memento of the occasion. The Secretary read the following list of names:

Dr Theodore Bacon
Dr Frederick S Burns
Dr Lincoln Davis
Dr Richard Elv
Dr Eugene E Everett
Dr Patrick A Grady
Dr Joseph F Howard
Dr Arthur C Nason
Dr Edwin B Nielsen
Dr Luther G Paul
Dr Ralph W Place
Dr Mortimer J Stoddard
Dr Frank T Woodbury

The President then called for the delegates from other New England State Societies. The delegate from Connecticut, Dr Robert A Goodell, was the only one present, and Dr Reardon invited him to the platform. Dr Goodell spoke as follows:

It is again a great honor and privilege to come here and to bring the greetings and cordial good wishes of the members of the Connecticut State Medical Society. Dr Sprague, the president-elect, and Dr Sam Harvey, the retiring president, have both sent their personal greetings, as well as Dr Creighton Barker, our executive secretary, and I am sure that I bring the good wishes of all the members of our society.

You have a fine program. I was here last year, and I enjoyed it so much that I finally teased them into sending me again.

The President called for Dr James Faulkner to come to the platform to present the Society awards to medical students. Dr Faulkner spoke as follows:

Last year the Society voted to award a prize to a fourth-year student in each of the medical schools in the Commonwealth who best exemplified the qualities that go to make up the good physician. The task and responsibility of selecting a prize and of selecting students to receive these prizes was turned over to the Committee on Medical Education, and I am speaking in behalf of Dr Keefer, the chairman of that committee, today. Dr Keefer had to be in western Ontario today.

In selecting a suitable prize, the Committee had a good deal of discussion, and I think were very fortunate in

what they were able to do. They decided that a book would be an appropriate prize, and they have selected a de luxe edition of the *Symposium of Hematology*, which was written in honor of Dr. George Minot, a distinguished member of this society, Nobel Prize winner, and each volume is appropriately inscribed by the officers of the Society and is autographed by Dr. Minot. This volume contains Dr. Minot's original work on the use of extract of liver in pernicious anemia. That was the easiest task of the committee.

Selecting the students who best exemplified the intangible qualities that make up a good physician was a very difficult task. The committee handed it over to the deans of the three medical schools, and I had to act in a dual capacity there. The deans, in turn, consulted with members of their faculties in an attempt to measure rather intangible values.

There were many, many students to whom these awards might have been made. I am sure that the students who are receiving them this morning are representative of the highest type of material that is being put out from the medical schools of the Commonwealth, and it gives me great pleasure to announce the recipients of these awards from Boston University, Sylvan Baer, from Harvard University, Henry S. Harvey, and from Tufts College, William H. Ellswood.

Dr. Reardon explained that the books were autographed by Dr. George Minot, and contained a bookplate signed by the president and the secretary of the Society.

Dr. Reardon presented a book to each of the three students. He then told the audience that a devoted fellow of the Society had donated a fund to be used, in succeeding years, to purchase similar awards.

The President then introduced the newly elected officers of the Society. To Dr. Arthur W. Allen, the new president, he presented a copy of Robert's *Rules of Order* and an inscribed gavel.

Dr. Allen thanked the President for the gifts and then told the meeting of his first technical error in not asking for approval of his appointments at the Council meeting the evening before. Motion was made from the floor to approve Dr. Allen's appointments. The motion was seconded, and it was so voted.

Dr. Reardon then introduced Dr. C. Sidney Burwell, dean of Harvard Medical School, who delivered the one hundred and forty-first annual oration, "Some Responsibilities of Medical Education."

At the close of the oration, Dr. Reardon declared the one hundred and sixty-eighth annual meeting adjourned at 12:45 p.m.

APPENDIX NO. 1

OFFICERS FOR 1949-1950

President Arthur W. Allen, Boston, 266 Beacon St.
President-Elect Leland S. McKittrick, Brookline, 1180 Beacon St.
Vice-President Albert A. Hornor, Brookline Office, Boston, 319 Longwood Ave.
Secretary H. Quimby Gallupe, Waltham Office, Boston, 8 Fenway.
Treasurer Eliot Hubbard, Jr., Cambridge, 29 Highland St.
Assistant Treasurer Norman A. Welch, West Roxbury Office, Boston, 520 Commonwealth Ave.
Orator John W. O'Meara, Worcester, 390 Main St.

COMMITTEES ELECTED BY THE DISTRICTS

Executive Committee of the Council — Established 1941 (members *ex-officio* and one councilor and alternate elected by the councilors of each district medical society)
PRESIDENT Arthur W. Allen, Boston, 266 Beacon St.
PRESIDENT-ELECT Leland S. McKittrick, Brookline, 1180 Beacon St.
VICE-PRESIDENT Albert A. Hornor, Brookline Office, Boston, 319 Longwood Ave.
SECRETARY H. Quimby Gallupe, Waltham Office, Boston, 8 Fenway.
TREASURER Eliot Hubbard, Jr., Cambridge, 29 Highland St.
ASSISTANT TREASURER Norman A. Welch, West Roxbury Office, Boston, 520 Commonwealth Ave.

Term Expires 1950

BERKSHIRE Helen M. Scoville, Pittsfield, Pittsfield General Hospital (Alternate C. T. Leslie, Pittsfield, 18 Bank Row).
FRANKLIN Lawrence R. Dame, Greenfield, 78 Federal St. (Alternate Frank W. Dean, East Northfield, 185 Main St.).
HAMPDEN Archibald J. Douglas, Westfield, 30 Court St. (Alternate Frederic Hagler, Springfield, 20 Maple St.).
MIDDLESEX NORTH William M. Collins, Lowell, 174 Central St. (Alternate Artemas J. Stewart, Lowell, 310 Merrimack St.).
NORFOLK Charles J. E. Kickham, Jamaica Plain Office, Brookline, 1101 Beacon St. (Alternate Carl Beare, Boston, 483 Beacon St.).
WORCESTER NORTH John J. Curley, Leominster, 89 West St. (Alternate George P. Keaveny, Fitchburg, 62 Fox St.).

Term Expires 1951

ESSEX SOUTH Albert E. Parkhurst, Beverly, 1 Monument Sq. (Alternate Edwin D. Reynolds, Danvers, 48 High St.).
HAMPSHIRE Maurice T. Kennedy, Hadley, 11 Middle St. (Alternate L. Beverley Pond, Easthampton, 115 Main St.).
MIDDLESEX SOUTH Joseph C. Merriam, Framingham, 198 Union Ave. (Alternate John F. Casey, Brighton Office, Boston, 475 Commonwealth Ave.).
NORFOLK SOUTH Robert L. Cook, Quincy, 1245 Hancock St. (Alternate William R. Helfrich, Quincy, 272 Southern Artery).
SUFFOLK Harvey A. Kelly, Winthrop, 200 Pleasant St. (Alternate William E. Browne, Boston, 587 Beacon St.).
WORCESTER John Fallon, Worcester, 10 Institute Rd. (Alternate Nicholas S. Scarcello, Worcester, 1 Seldon St.).

Term Expires 1952

BARNSTABLE Harold F. Rowley, Harwichport. (Alternate Donald E. Higgins, Cotuit, Main St.).
BRISTOL NORTH William M. Stobbs, Attleboro, 63 Bank St. (Alternate Milton E. Johnson, Attleboro, 33 Bank St.).
BRISTOL SOUTH Curtis C. Tripp, New Bedford, 416 County St. (Alternate John C. Corrigan, Fall River, 422 North Main St.).
ESSEX NORTH Arnold P. George, Haverhill, 31 Summer St. (Alternate Frederic N. Sweetser, Merrimac, 19 Main St.).
MIDDLESEX EAST Thomas P. Devlin, Stoneham, 34 Pleasant St. (Alternate Robert Dutton, Wakefield, 33 Avon St.).
PLYMOUTH Charles D. McCann, Brockton, 12 Cottage St. (Alternate Alton L. Hurlburt, East Bridgewater, 81 Central St.).

Subcommittee on Blue Cross-Blue Shield Problems

Charles J. E. Kickham, Norfolk, *chairman*, Paul M. Butterfield, Barnstable, John Fallon, Worcester, Harvey A. Kelly, Suffolk, Joseph C. Merriam, Middlesex South.

Committee on Nominations — Established 1874 (one councilor and alternate elected yearly by each district medical society)

BARNSTABLE Harold F. Rowley, Harwichport. (Alternate Donald E. Higgins, Cotuit, Main St.).
BERKSHIRE Helen M. Scoville, Pittsfield, Pittsfield General Hospital (Alternate C. T. Leslie, Pittsfield, 18 Bank Row).

BRISTOL NORTH Joseph L. Murphy, Taunton 23 Cedar St (Alternate Curtis B. Kingsbury, Taunton 65 Prospect St.)

BRISTOL SOUTH Harold E. Perry, New Bedford 159 Cottage St (Alternate William Mason, Fall River, 151 Rock St.)

ESSEX NORTH Charles F. Warren Amesbury 155 Main St (Alternate Percy J. Look, Andover, 115 Main St.)

ESSEX SOUTH DeWitt S. Clark, Salem, 2 Oliver St (Alternate Harrison G. Pope, Swampscott, 90 Humpbrex St.)

FRANKLIN Warren D. Thomas Montague Central St. (Alternate Kenneth H. Rice, South Deerfield 141 Main St.)

HAMPDEN George L. Schadt, Springfield, 44 Chestnut St. (Alternate George L. Steele, Springfield 20 Maple St.)

HAMPSHIRE Joseph R. Hobbs, Williamsburg, Main St. (Alternate L. Beverley Pond, Easthampton, 115 Main St.)

MIDDLESEX EAST Edward M. Halligan Reading 37 Salem St. (Alternate John M. Wilcox, Woburn, 6 Bennet St.)

MIDDLESEX NORTH James Y. Rodger, Lowell, 226 Central St. (Alternate William M. Collins, Lowell 174 Central St.)

MIDDLESEX SOUTH (Alternate Fred R. Jouett, Cambridge, 1 Craigie St.)

NORFOLK Albert Ehrenfried, Boston, 520 Beacon St. (Alternate Carleton E. Allard, Dorchester, 428 Columbia Rd.)

NORFOLK SOUTH Nabum R. Pillsbury, South Braintree, Norfolk County Hospital (Alternate William R. Helfrich, Quincy, 272 Southern Artery.)

PLYMOUTH Peirce H. Leavitt, Brockton 147 West Elm St. (Alternate John C. Angley, Brantville, School St.)

SUFFOLK Conrad Wesselboeft, Boston 315 Marlboro St. (Alternate Charles C. Lund, Boston, 20 Gloucester St.)

WORCESTER Frank B. Carr, Worcester 27 Elm St. (Alternate George W. Ballantine, Worcester, 27 Elm St.)

WORCESTER NORTH John J. Curley, Leominster 89 West St. (Alternate Clarence A. McPeak, Fitchburg 18 Hartwell St.)

Committee on Public Relations — Established 1939 (one councilor elected yearly by each district medical society, the president and president-elect of the Society are chairman and vice-chairman respectively, and the vice-president and secretary of the Society are members *(ex-officio)*)

BARNSTABLE Harold F. Rowley, Harwichport

BERKSHIRE Patrick J. Sullivan, Dalton, 471 Main St

BRISTOL NORTH Milton E. Johnson, Attleboro, 53 Bank St

BRISTOL SOUTH Milton T. MacDonald, New Bedford, 99 Clinton St

ESSEX NORTH Harold R. Kurth, Lawrence, 57 Jackson St

ESSEX SOUTH Bernard Appel Lynn 261 Ocean St

FRANKLIN John E. Moran, Greenfield 15 Franklin St

HAMPDEN Frederic Hagler, Springfield, 20 Maple St

HAMPSHIRE Joseph R. Hobbs, Williamsburg, Main St

MIDDLESEX EAST Milton J. Quinn, Winchester, 44 Church St

MIDDLESEX NORTH Samuel A. Dibbins, Lowell 528 Andover St

MIDDLESEX SOUTH Ralph H. Wells Lexington 1430 Massachusetts Ave

NORFOLK Dean S. Luce, Canton 553 Washington St

NORFOLK SOUTH Henry A. Robinson Hingham, 205 North St

PLYMOUTH Charles D. McCann, Brockton, 12 Cottage St

SUFFOLK G. Lande Gately East Boston, 624 Bennington St

WORCESTER Nicholas S. Scarcello Worcester 1 Seiden St

WORCESTER NORTH James A. McHugh Leominster, 55 West St

Subcommittees of Committee on Public Relations

TAX-SUPPORTED MEDICAL CARE — Established 1940
Albert A. Hornor Suffolk *chairman*, William W. Babson, Essex South, Donald Hight Worcester, Francis P. McCarthy, Norfolk

COMMITTEE TO MEET WITH THE MEDICAL ADVISORY COMMITTEE OF THE INDUSTRIAL ACCIDENT BOARD — Established 1942

Gordon Morrison, Middlesex South *chairman*, Charles H. Bradford, Suffolk, Joseph H. Burnett, Middlesex South, Somers Fraser Suffolk, William W. Teahan, Hampden

Committee on Legislation — Established 1942 (one councilor elected yearly by each district medical society)

BARNSTABLE Julius G. Keller, Pocasset, Barnstable County Sanatorium

BERKSHIRE Modestino Criscitello, Pittsfield, 28 North St.

BRISTOL NORTH William M. Stobbs, Attleboro, 63 Bank St.

BRISTOL SOUTH Daniel F. Gallery, Fall River, 151 Rock St.

ESSEX NORTH John T. Batal Lawrence, 281 Haverhill St.

ESSEX SOUTH Leonard F. Box, Beverly, 39 Broadway

FRANKLIN Harold H. Mahar, Orange, 1 High St.

HAMPDEN Alfred M. Glickman, Springfield, 285 Longbill St.

HAMPSHIRE Justin E. Hayes, Amherst Office, Northampton

16 Center St

MIDDLESEX EAST Justin L. Anderson, Reading, 55 Woburn St.

MIDDLESEX NORTH Joseph D. Sweeney, Lowell, 174 Central St.

MIDDLESEX SOUTH John F. Casey Allston Office, Boston,

475 Commonwealth Ave

NORFOLK Solomon L. Skvirsky Boston 545 State House

NORFOLK SOUTH David L. Belding Boston, 80 East Concord St.

PLYMOUTH Harold H. Hamilton Plymouth 70 Court St.

SUFFOLK William E. Browne, Boston 587 Beacon St.

WORCESTER John B. Butts Worcester 24 Franklin St.

WORCESTER NORTH Joseph P. Marnanc, Gardner, 4 Comee St.

Subcommittee of the Committee on Legislation

NATIONAL LEGISLATION — Established 1946

Charles G. Hayden Norfolk *chairman*, Elmer S. Bagnall,

Essex North, David L. Belding, Norfolk South,

Vlado A. Getung, Middlesex South, Augustus

Thorndike, Suffolk, William H. Sweet, Suffolk

STANDING COMMITTEES FOR 1949-1950

ELECTED BY THE COUNCIL MAY 23, 1949

Publications — Established 1825

Richard M. Smith, Suffolk June 6, 1933 (appointed chairman May 21, 1941)

Oliver Cope, Middlesex South May 21, 1941

John Fallon Worcester November 14, 1944

James P. O'Hare Suffolk June 9, 1936

Conrad Wesselboeft, Suffolk June 2, 1937

Arrangements — Established 1849

Franklin G. Balch, Jr., Suffolk May 19, 1947 (appointed chairman May 23, 1949)

Gordon A. Donaldson, Middlesex South May 19, 1947

John W. Norcross Middlesex South May 19, 1947

Albert Ehrenfried Norfolk May 24, 1948

James A. Halsted, Norfolk May 23, 1949

Ethics and Discipline — Established 1871

Ralph R. Stratton, Middlesex East June 9, 1936 (appointed chairman May 21, 1941)

William J. Brickley, Suffolk February 3, 1947

Archibald R. Gardner, Middlesex North May 21, 1949

Allen G. Rice, Hampden June 1, 1938

James H. Townsend, Middlesex South May 23, 1949

Medical Education — Established 1881

Chester S. Keefe, Suffolk February 4, 1942 (appointed chairman May 19, 1947)

Oliver Cope, Middlesex South May 23, 1949

James M. Faulkner, Norfolk May 21, 1946

Isaac R Jankelson, Norfolk May 25, 1942
Robert T Monroe, Norfolk May 23, 1949

Advisory Subcommittee on Medical Education — Established 1948

Isaac R Jankelson, Norfolk October 6, 1948 (chairman)
George E Gardner, Middlesex South October 6, 1948
William A Hinton, Suffolk October 6, 1948
C Guy Lane, Middlesex South October 6, 1948
George W Thorn, Suffolk May 23, 1949
Augustus Thorndike, Suffolk October 6, 1948

Membership — Established 1897

Lewis S Pilcher, Middlesex South July 26, 1946 (appointed chairman May 24, 1948)
William A R Chapin, Hampden May 23, 1945
Henry F Howe, Norfolk South May 23, 1949
Donald Munro, Suffolk May 23, 1949
Samuel N Vose, Suffolk March 15, 1944
(John W McKeon, Worcester, C T Leslie, Berkshire, Kathlyne S Snow, Norfolk, — representing the Supervising Censors)

Public Health — Established 1912

Roy J Ward, Worcester May 22, 1944 (chairman)
Alfred E Frechette, Norfolk May 23, 1949
John J Poutas, Middlesex South May 21, 1946
Warren R Sisson, Suffolk May 19, 1947
Conrad Wesselhoeft, Suffolk July 27, 1944

Subcommittee of the Committee on Public Health

MENTAL HEALTH — Established 1947
Walter E Barton, Norfolk February 5, 1947 (chairman)
G Colket Caner, Suffolk May 23, 1949
William Malamud, Worcester February 5, 1947
Francis M Rackemann, Suffolk May 23, 1949
Henry A Tadgell, Hampshire February 5, 1947

Medical Defense — Established 1927

Horatio Rogers, Suffolk June 7, 1939 (appointed chairman May 19, 1947)
Charles B Burbank, Norfolk May 23, 1949
John E Moran, Franklin May 19, 1947
Charles J Kickham, Norfolk May 21, 1946
William R Morrison, Suffolk June 9, 1936

Finance — Established 1938

Robert W Buck, Middlesex South May 21, 1946 (chairman)
Henry H Faxon, Norfolk May 23, 1949
Francis C Hall, Suffolk July 8, 1943
Fabyan Packard, Middlesex South May 21, 1946
Bancroft C Wheeler, Worcester May 21, 1946

Society Headquarters — Established 1942

Frank R Ober, Suffolk May 22, 1944 (appointed chairman Nov 1, 1944)
Joseph S Barr, Middlesex South May 23, 1949
Albert A Horner, Suffolk November 6, 1944
Dwight O'Hara, Middlesex South May 23, 1949
Walter G Phippen, Essex South May 21, 1946

Industrial Health — Established 1942

Henry C Marhle, Suffolk May 19, 1947 (appointed chairman May 23, 1949)
Karl T Benedict, Worcester May 23, 1949
Harriet L Hardy, Middlesex South May 23, 1949

Daniel L Lynch, Norfolk May 25, 1942
George E Morris, Norfolk May 23, 1949
John J Poutas, Middlesex South May 23, 1949
George F Wilkins, Norfolk May 23, 1949

Advisory Committee to Committee on Industrial Health — Established 1942

Albert O Seeler
William H Seymour
Emma S Tousant

Benevolence — Established 1948

Dwight O'Hara May 24, 1948 (chairman)
Middlesex South
Theodore L Badger, Norfolk May 24, 1948
Robert W Buck, Middlesex South May 24, 1948
Eliot Hubbard, Jr., Middlesex South May 24, 1948
Charles C Lund, Suffolk May 24, 1948

Council Rules and By-Laws — Established 1948

Edward P Bagg, Hampden October 6, 1948 (chairman)
Elmer S Bagnall, Essex North October 6, 1948
Albert A Horner, Suffolk October 6, 1948
Frank R Ober, Suffolk October 6, 1948

SPECIAL COMMITTEES FOR 1949-1950

ELECTED BY THE COUNCIL, MAY 23, 1949

Cancer — Established 1947

Ernest M Daland, Suffolk, *chairman*, Thomas J Anglem, Suffolk, Charles C Lund, Suffolk, Channing C Simmons, Suffolk, Shields Warren, Suffolk

To Meet with the Massachusetts Hospital Association — Established 1940

Albert E Parkhurst, Essex South, *chairman*, Joseph A Holmes, Middlesex South, Storer P Humphreys, Essex South, Harvey Morrison, Norfolk, Donald A Nickerson, Middlesex East, Nicholas S Scarcello, Worcester, Sidney C Wiggins, Suffolk

Maternal Welfare — Established 1941

Duncan Reid, Middlesex South, *chairman*, James M Baty, Middlesex South, Arthur F G Edgelow, Hampden, Samuel Kirkwood, Middlesex East, Florence L McKay, Suffolk, Louis E Phaneuf, Suffolk, Raymond S Titus, Norfolk

Postgraduate Medical Education — Established 1944

W Richard Ohler, Norfolk, *chairman*, James T Brosnan, Worcester, John F Conlin, Suffolk, Harwood W Cummings, Franklin, John E Dunphy, Norfolk, Vlado A Getting, Middlesex South, Robert H Goodwin, Bristol South, Harold H Hamilton, Plymouth, Lewis M Hurxthal, Suffolk, Allen S Johnson, Hampden, Eric F Joslin, Berkshire, George P Keaveny, Worcester North, Samuel H Proger, Norfolk, Frederick R Radcliffe, Essex North, Duncan E Reid, Middlesex South, Harry C Solomon, Suffolk, Henry D Stehbins, Essex South, Richard P Stetson, Norfolk, Thomas J G Tighe, Middlesex North, Claude E Welch, Middlesex South, Hilary F White, Bristol South

Medical Economics — Established 1944

Elmer S Bagnall, Essex North, *chairman*, Harold M Frost, Suffolk, Vlado A Getting, Middlesex South, Hugh R Leavell, Middlesex South, Henry A Robinson, Norfolk South

To Make Recommendations as to Future Directors of Blue Shield — Established 1945

Pierce H Leavitt, Plymouth, *chairman* (term expires 1950), Elliott P Joslin, Suffolk, (term expires 1952), Thomas H Lanman, Suffolk, (term expires 1954), George G Smith, Norfolk, (term expires 1953)

To Meet with the Director of Veterans Administration Medical Care for Veterans and Their Dependents — Established 1945

Humphrey L. McCarthy, Norfolk, *chairman*, James K. Bragger, Norfolk, Allen S. Johnson, Hampden

Postgraduate Assembly — Established 1946

Richard P. Stetson, Norfolk, *chairman*, Theodore L. Badger, Norfolk, Joseph S. Barr, Middlesex South, John F. Casey, Middlesex South, John F. Conlin, Suffolk, T. Hale Ham, Suffolk, Chester S. Keefer, Suffolk, Alexander A. Levi, Middlesex South, James Z. Naurison, Hampden, John W. Norcross, Middlesex South, W. Richard Ohler, Norfolk, Leroy E. Perkins, Suffolk, Claude E. Welch, Middlesex South

School Health — Established 1947

Ernest M. Morris, Middlesex South, *chairman*, Stewart H. Clifford, Middlesex South, Allan R. Cunningham, Middlesex East, Reginald Fitz, Suffolk, Joseph Garland, Suffolk, Kenneth L. MacLachlan, Middlesex East, Thomas F. Reilly, Hampden

Auditing

Howard B. Jackson, Norfolk, *chairman*, Frank T. Downey, Middlesex South

Advisory Council to Women's Auxiliary — Established 1948

John F. Conlin, Suffolk, *chairman*, David L. Belding, Norfolk South, Milton J. Quinn, Middlesex East.

Advisory Committee for Red Cross Blood Bank — Established 1948

Lamar Soutter, Suffolk, *chairman*, F. Harold Allen, Jr., Middlesex South, Stephen Brown, Hampshire, Charles P. Emerson, Jr., Norfolk, Harold B. Kenton, William C. Moloney, Norfolk, Joseph F. Ross, Suffolk

Advisory Committee on Malpractice Insurance — Established 1948

Carl Bearse, Norfolk, *chairman*, William J. Brickley, Suffolk, Maurice Fremont-Smith, Suffolk, Charles D. McCann, Plymouth, Horatio Rogers, Suffolk

Emergency Medical Service — Established 1948

Thomas H. Lanman, Suffolk, *chairman*, Charles H. Bradford, Suffolk, Edward D. Churchill, Middlesex South, Donald E. Currier, Suffolk, Eugene C. Eppinger, Norfolk, J. Roswell Gallagher, Essex North, Allen S. Johnson, Hampden

Representatives to the Massachusetts Central Health Council

Elmer S. Bagnall, Essex North, *chairman*, James W. Bunce, Berkshire, Merrill E. Champion, Suffolk, Earle M. Chapman, Suffolk, Paul Nathan, Hampden, Roy J. Ward, Worcester

Representatives to the Hospital Presidents Association

H. Quimby Gallupe, Middlesex South, John W. Spellman, Norfolk

Representative on the Legislative Committee of the Massachusetts Central Health Council

John F. Conlin, Suffolk

Representative on a Professional Advisory Committee Organized by the Division of Vocational Rehabilitation of the State Department of Education for the Purpose of Establishing a Program of Physical Restoration

Augustus Thorndike, Suffolk

Representatives to the Council of the New England State Medical Societies

William A. R. Chapin, Hampden, Gerald N. Hoeffel, Middlesex South, Norman A. Welch, Norfolk

Representative to the Hospital Council of Boston for the Year

William E. Browne, Suffolk

Twenty-Five Voting Members in Massachusetts Hospital Service, Inc.

Richard B. Butler, Bristol South, Laurence D. Chapin, Hampden, Lucien R. Chaput, Essex North, Henry W. Godfrey, Middlesex South, Harold H. Hamilton, Plymouth, Roy J. Heffernan, Norfolk, Albert A. Hornor, Suffolk, Harold R. Kurth, Essex North, Benjamin deF. Lambert, Middlesex North, Alexander A. Levi, Middlesex South, Joseph C. Merriam, Middlesex South, Albert M. Moloney, Norfolk, Donald Munro, Suffolk, Donald A. Nickerson, Middlesex East, James P. O'Hare, Suffolk, Albert E. Parkhurst, Essex South, Lewis S. Pilcher, Middlesex South, Helen S. Pittman, Suffolk, Allen G. Rice, Hampden, Laurence L. Robbins, Middlesex East, Arthur T. Ronan, Norfolk, Walter L. Sargent, Norfolk South, Monroe J. Schlesinger, Middlesex South, George L. Steele, Hampden, Sidney C. Wiggins, Suffolk

Diabetes

Howard F. Root, Suffolk, *chairman*, Frank N. Allan, Middlesex South, George Ballantine, Worcester, Joseph Rosenthal, Norfolk, James L. Smead, Hampden, James H. Townsend, Middlesex South, Priscilla White, Suffolk

To Meet with the Massachusetts Nurses Association

Richard B. Cattell, Suffolk, *chairman*, David L. Belding, Norfolk South, Joseph A. Holmes, Middlesex South, Peirce H. Leavitt, Plymouth, Samuel Proger, Norfolk, William F. Wood, Middlesex South

Veterans Affairs

Harvey A. Kelly, Suffolk, *chairman*, John M. Barry, Essex North, Samuel Bachrach, Worcester, Kenneth A. Brown, Middlesex South, John F. Conlin, Suffolk, James M. Faulkner, Norfolk, George S. Reynolds, Berkshire

Veterans Administration Board of Review

James K. Bragger, Norfolk, *chairman*, Edward P. Bagg, Hampden, John F. Conlin, Suffolk, Timothy F. P. Lyons, Norfolk, Humphrey L. McCarthy, Norfolk

To Meet with the Officers of the Bay State Medical Rehabilitation Center

Charles H. Bradford, Suffolk, *chairman*, Alexander P. Aitken, Middlesex East, Joseph S. Barr, Middlesex South, Walter Bauer, Suffolk, Herrman L. Blumgart, Suffolk, W. Irving Clark, Worcester, Otto J. Hermann, Norfolk, Arthur L. Watkins, Middlesex South

Advisory Board — Established 1949

Daniel B. Reardon, Edward P. Bagg, Dwight O'Hara, Reginald Fitz, Elmer S. Bagnall

Chairman of the Blue Shield Fee Committee Chairmen

Richard H. Sweet, Suffolk

Co-Ordinating Committee — Established 1949

Frank H. Lahcy, Suffolk, *chairman*, Charles J. Kichham, Norfolk, Leland S. McKittrick, Suffolk, Patrick J. Sullivan, Berkshire, John J. Curley, Worcester North, Walter G. Phippen, Essex South, Frank W. Snow, Essex North, Earle M. Chapman, Suffolk, Daniel B. Reardon, Norfolk South, Arthur W. Allen, Suffolk, Albert A. Hornor, Suffolk, H.

Quimby Gallupe, Middlesex South, Eliot Hubbard, Jr., Middlesex South, Norman A Welch, Norfolk, Elmer S Bagnall, Essex North, Charles G Hayden, Norfolk, David L Belding, Norfolk South, Vlado A Getting, Middlesex South, Augustus Thorndike, Suffolk, William H Sweet, Suffolk, Henry A Robinson, Norfolk South, Harold R Kurth, Essex North, Curtis C Tripp, Bristol South, Joseph Garland, Suffolk

DELEGATES AND ALTERNATES TO THE HOUSE OF DELEGATES OF THE AMERICAN MEDICAL ASSOCIATION FOR 1949-1950

Delegates

Alternates

June 1, 1947, to January 1, 1950

Charles J Kickham,
Norfolk
Leland S McKittrick,
Suffolk

John Fallon,
Worcester
Harold R Kurth,
Essex North

June 1, 1948, to January 1, 1951

Patrick J Sullivan,
Berkshire
John J Curley,
Worcester North
Walter G Phippen,
Essex South
Frank W Snow,
Essex North

Nahum R Pillsbury,
Norfolk South
Patrick E Gear,
Hampden
John I B Vail,
Barnstable
Frederick Hinchliffe,
Norfolk South

June 1, 1949, to January 1, 1952

Earle M Chapman,
Suffolk

Benjamin deF Lambert,
Middlesex North

DELEGATES TO NEW ENGLAND STATE MEDICAL SOCIETIES

Maine	Samuel H Proger, Norfolk
New Hampshire	John D Adams, Essex South Storer P Humphreys, Essex South
Vermont	Frank R Ober, Suffolk Sidney L Morrison, Middlesex South
Rhode Island	William Mason, Bristol North Ernest M Daland, Suffolk
Connecticut	Allen G Rice, Hampden Thomas H Lanman, Suffolk

COUNCILORS FOR 1949-1950

(ELECTED BY THE DISTRICT MEDICAL SOCIETIES AT THEIR ANNUAL MEETINGS, APRIL 15 TO MAY 15, 1949)

Barnstable

A J D'Elia, Harwichport, Main St, V P
D E Higgins, Cotuit, Main St, A E C, A M N C
S L Hunt, Yarmouthport, Grand Army Highway, Sec
J G Kelley, Pocasset, Barnstable County Sanatorium,
Leg C
H F Rowley, Harwichport, E C, M N C, P R C

Berkshire

N B McWilliams, Williamstown, 56 Spring St, V P
D N Beers, Pittsfield, 74 North St, Sec
Modestino Criscitello, Pittsfield, 29 North St, Leg C
Antoine Dumouchel, North Adams, 56 Summer St
C F Fasce, Pittsfield, 311 North St
J H Fierman, Pittsfield, 74 North St
C T Leslie, Pittsfield, 18 Bank Row, A M N C,
A E C
Percie Roberts, Sheffield, Main St.
Helen M Scoville, Pittsfield, Pittsfield General Hosp,
E C, M N C
P J Sullivan, Dalton, 471 Main Street, P R C

Bristol North

J H Brewster, Attleboro, 178 South Main St, V P
C N Burden, Taunton, 3 Prospect St, Sec
M E Johnson, Attleboro, 33 Bank St, P R C, A E C
C B Kingsbury, Taunton, 63 Prospect St, A M N C
J L Murphy, Taunton, 23 Cedar St, M N C
W M Stobbs, Attleboro, 63 Bank St, E C, Leg C

Bristol South

J S C Fielden, Jr., Fall River, 177 Winter St, V P
R B Butler, Fall River, 278 North Main St.
J C Corrigan, Fall River, 422 North Main St, A E C
J E Fell, Fall River, 181 Purchase St, Sec
D F Gallery, Fall River, 151 Rock St, Leg C
E D Gardner, Marion, Box 175
R H Goodwin, New Bedford, 15 South 6th St
M T MacDonald, New Bedford, 99 Clinton St, P R C
William Mason, Fall River, 151 Rock St, A M N C
D R Mills, Edgartown, Pease Point Way
H E Perry, New Bedford, 159 Cottage St, M N C
C C Persons, New Bedford, 118 Cottage St
A J Pothier, New Bedford, 720 County St.
C C Tripp, New Bedford, 416 County St., E C
Henry Wardle, Fall River, 173 Purchase St.

Essex North

Z W Colson, Lawrence, 301 Essex St, V P
M F Ames, Newburyport, Box 88
E S Bagnall, Groveland, 281 Main St., Ex-Pres
W J Bain, Lawrence, 477 Essex St
J T Batal, Lawrence, 281 Haverhill St. Leg C
J F Curtin, Lawrence, 281 Haverhill St.
A P George, Haverhill, 32 Summer St., E C
H R Kurth, Lawrence, 57 Jackson St, Sec, P R C
P J Look, Andover, 115 Main St, A M N C
R C Norris, Methuen, 247 Broadway
L C Pearce, Newburyport, 279 High St
F W Snow, Newburyport, 24 Essex St
F N Swetsir, Merrimac, 19 Main St, A E C
C F Warren, Amesbury, 1 School St, M N C
C A Weiss, Lawrence, 160 Jackson St
J F Whitten, Amesbury, 448 Main St

Essex South

C F Twomey, Lynn, 80 Ocean St, V P
Bernard Appel, Lynn, 281 Ocean St, P R C
W D Babb, Salem, 40 Chestnut St
W W Babson, Gloucester, 79 Prospect St
L F Box, Beverly, 39 Broadway, Leg C
D S Clark, Salem, 2 Oliver St, M N C
Gerard Cote, Salem, 1 Harbor St
J J Crowley, Lynn, 65 Broad St
J H Fine, Beverly, 26 Abbott St
T H Foote, Ipswich, 2 North Main St
L C Furbush, Saugus, 420 Lincoln Ave
S N Gardner, Salem, 24 Chestnut St
F P Morse, Jr., Salem, 35 Summer St
A E Parkhurst, Beverly, 1 Monument Sq, E C
M H Pett, Gloucester, 54 Middle St
W G Phippen, Salem, 31 Chestnut St, Ex-Pres
H G Pope, Swampscott, 90 Humphrey St, A M N C
E D Reynolds, Danvers, 48 High St, A E C
H D Stebbins, Salem, 342 Essex St, Sec
Barnett Weinstein, Peabody, 45 Washington St
R J Williams, Lynn, 39 Lynn Shore Drive

Franklin

L R Dame, Greenfield, 78 Federal St, V P, E C
F W Dean, East Northfield, 185 Main St, A E C
H H Mahar, Orange, 1 High St, Leg C
J E Moran, Greenfield, 15 Franklin St, P R C
K H Rice, South Deerfield, 141 Main St, A M N C
M M Sisson, Greenfield, 31 Federal St., Sec
W D Thomas, Montague, Central St, M N C

Hampden

A H Riordan, Indian Orchard, 147 Oak St, V P
M S Allan, Springfield, 127 Maple St
E P Bagg, Holyoke, 207 Elm St., Ex-Pres

R L Barrett, Springfield, 21 Maple St
 J M Birnie, Springfield, 146 Chestnut St., Ex-Pres
 M J Carian, Springfield, 115 State St
 W A R Chapin, Springfield, 121 Chestnut St
 J L Chereskin, Springfield, 333 Bridge St
 A J Douglas, Westfield, 30 Court St, E C
 E C Dubois, Springfield, 20 Maple St
 Adolph Franz, Jr, Holyoke, 1158 Northampton St
 P E Gear, Holyoke, 188 Chestnut St
 J M Gilchrist, Springfield, 121 Chestnut St
 A M Glickman, Springfield, 283 Longhill St., Leg C
 Frederic Hagler, Springfield, 20 Maple St, P R C,
 A E C
 D R Hayes, Springfield, 72 Harvard St
 W J Kiesel, Springfield, 1570 Main St
 John Pallo, Westfield, 97 Elm St
 S F Potsbury, Holyoke, 323 Appleton St
 L A Putnam, Holyoke, 399 Appleton St
 A G Rice, Springfield, 33 School St., Sec
 G L Schadt, Springfield, 44 Chestnut St., M N C,
 Ex-Pres
 J A Seaman, Springfield, 20 Maple St
 H N Simpson, Springfield, 276 Bridge St
 G L Steele, Springfield, A M N C

Hampshire

E J Manwell, Northampton, 16 Centre St., V P
 R S Clapp, Amherst, 110 North Pleasant St
 J E Hayes, Northampton, 16 Centre St., Leg C
 J R Hobbs, Williamsburg, Main St, P R C, M N C
 M T Kennedy, Hadley, 11 Middle St., E C
 J G Pekala, Northampton, 245 Main St
 L B Pond, Easthampton, 115 Main St., A E C,
 M N C
 Mary P Snook, Northampton, Northampton State
 Hosp., Sec

Middlesex East

I W Richardson, Wakefield, 21 Yale Ave., V P
 J L Anderson, Reading, 53 Woburn St., Leg C
 T P Devlin, Stoneham, 38 Pleasant St., E C
 Robert Dutton, Wakefield, 33 Avon St., A E C
 E M Halligan, Reading, 37 Salem St., M N C
 R W Lavton, Melrose, 8 Porter St., Sec
 K L MacLachlan, Melrose, 1 Bellevue Ave
 H L Mueller, Winchester, 31 Church St
 M J Quinn, Winchester, 44 Church St., P R C
 R R Stratton, Melrose, 538 Lynn Fells Parkway, C
 J M Wilcox, Woburn, 6 Bennett St., A M N C

Middlesex North

H R Coburn, Lowell, 202 Merrimack St., V P
 P G Berman, Lowell, 174 Central St., Sec
 W M Collins, Lowell, 174 Central St., E C, A M N C
 S A Dibbins, Lowell, 528 Andover St., P R C
 L J Hall, Lowell, 8 Merrimack St
 L F King, Lowell, 308 Merrimack St
 J Y Rodger, Lowell, 226 Central St., M N C
 A J Stewart, Lowell, 310 Merrimack St., A E C
 J D Sweeney, Lowell, 174 Central St., Leg C
 H A Titus, Lowell, 56 Holyrood Ave

Middlesex South

J M Baty, Belmont Office, Brookline, 1101 Beacon St.,
 V P
 G G Bailey, Belmont Office, Boston, 412 Beacon St
 E W Barron, Malden Office, Boston, 20 Ash St.
 Harris Bass, Everett, 351 Broadway
 J D Bennett, West Somerville, 72 College Ave
 L A Blacklow, Belmont, 100 Leonard St.
 W O Blanchard, Newton, 465 Centre St
 H K Bloom, Everett, 834 Broadway
 G F H Bowers, Newton Highlands, 156 Woodward St.
 Alice M Broadhurst, Watertown, 259 Mt. Auburn St
 Madelaine R Brown, Cambridge Office, Boston, 264
 Beacon St
 R N Brown, Malden, 621 Main St
 R W Buck, Waban Office, Boston, 5 Bay State Rd., C
 E J Butler, Cambridge, 25 Garden St
 J F Casey, Allston Office, Boston, 475 Commonwealth
 Ave., A E C, Leg C

C W Clark, Newtonville, 363 Walnut St
 E A Cooney, Newton Office, Boston, 270 Common-
 wealth Ave
 Oliver Cope, Cambridge Office, Boston, Mass General
 Hospital
 W H Crosby, Brighton, 304 Faneuil St.
 H J Crumb, Lexington, 1632 Massachusetts Ave
 J A Daley, Natick, 36 Pond St
 C L Derick, Newton Highlands Office, Boston, 412
 Beacon St.
 J G Downing, Newton Office, Boston, 520 Common-
 wealth Ave
 D J Duggan, Malden, 3 Hawthorne St
 A G Engelbach, Cambridge, 330 Mt. Auburn St
 W C Feeley, Cambridge, 859 Massachusetts Ave
 C W Finnerty, Somerville, 440 Broadway
 J M Flynn, Belmont Office, Boston, 412 Beacon St
 H Q Gallupe, Waltham Office, Boston, 8 Fenway,
 Secretary
 V A Getting, Belmont Office, Boston, 546 State House
 H A Godfrey, Auburndale, 14 Hancock St
 J D Golden, Medford, 86 Forest St
 A D Guthrie, Medford, 409 Salem St
 W T Hood, Hudson, 20 Lincoln St.
 Eliot Hubbard, Jr, Cambridge, 29 Highland St.,
 Treasurer
 A M Jackson, Everett, 312 Broadway
 F R Joutt, Cambridge, 1 Craigie St., A M N C
 S B Kelley, West Newton Office, Boston, 412 Bea-
 con St
 L G Kendall, Framingham, 198 Union Ave
 H A Kontoff, Newton Centre Office, Boston, 479
 Beacon St
 J J Lepore, Marlboro, 96 West Main St
 A A Levi, Newton Office, Boston, 481 Beacon St., Sec
 H E MacMahon, Cambridge Office, Boston, 416
 Huntington Ave
 A N Makeehnic, Cambridge, 14 Upland Rd
 R A McCarty, Waltham, 465 Lexington St.
 J H McSweeney, Somerville, 26 Bow St
 J C Merriam, Framingham, 198 Union Ave., E C
 Dudley Merrill, Cambridge, 51 Brattle St
 C E Mongan, Somerville, 24 Central St., Ex-Pres
 G M Morrison, Waban Office, Boston, 520 Common-
 wealth Ave
 D G Nutter, Newton Centre, 1094 Centre St
 Dwight O'Hara, Waltham Office, Boston, 416 Hunting-
 ton Ave., Ex-Pres
 Fabran Packard, Belmont, 154 Washington St
 L S Pilcher, Newton Centre Office, Brookline, 1180
 Beacon St., C
 Randolph Piper, Concord, 14 Sudbury Rd
 Max Ritvo, Newton Office, Boston, 416 Marlboro St
 L G Rondeau, Brighton, 555 Washington St
 G A Saunders, Arlington, 50 Pleasant St.
 M J Schlesinger, Newton Office, Boston, 330 Brook-
 line Ave
 S M Simons, Arlington, 1250 Massachusetts Ave
 E W Small, Belmont, 68 Leonard St
 H P Stevens, Cambridge, 1 Craigie St
 A B Toppan, Watertown, 289 Mt. Auburn St.
 J H Townsend, Cambridge, 330 Mt. Auburn St.
 J E Vance, Natick Office, Boston, 29 Bay State Rd
 C F Walcott, Cambridge, 81 Sparks St
 R H Wells, Lexington, 1430 Massachusetts Ave.,
 P R C
 B M Wein, Newton Office, 471 Commonwealth Ave
 Alfred Worcester, Waltham, 314 Bacon St., Ex-Pres
 Johannes Zovickian, Watertown, 528 Mt. Auburn St

Norfolk

W R Ohler, Jamaica Plain Office, Boston, 319 Long-
 wood Ave., V P
 A A Abrams, Brookline, 1093 Beacon St
 C E Allard, Dorchester, 428 Columbia Rd., A M N C
 B E Barton, West Roxbury, 10 Richwood St., Sec
 Carl Bearse, Boston, 483 Beacon St., A E C
 Elizabeth Broyles, Wellesley, Simpson Infirmary
 J H Caulcy, Dorchester, 8 Carruth St
 G L Doherty, West Roxbury Office, Boston, 466 Com-
 monwealth Ave

Albert Ehrenfried, Brookline Office, Boston, 520 Beacon St, M N C
 J M Faulkner, Brookline Office, Boston, 80 East Concord St.
 P S Foisie, Milton, 65 Hillview Road
 Susannah Friedman, Roxbury Office, Boston, 485 Commonwealth Ave
 T R Goethals, Brookline, 34 Hawthorn Rd
 D L Halbersleben, Brookline, 42 Goodnough Rd
 J A Halsted, Dedham Office, Jamaica Plain, Faulkner Hospital
 H B Harris, Dorchester, 487 Columbia Rd
 C G Hayden, Brookline Office, Boston, 38 Chauncy St
 R J Heffernan, Jamaica Plain Office, Brookline, 1101 Beacon St
 P J Jakmauh, Milton Office, South Boston, 300 Broadway
 I R Jankelson, Jamaica Plain Office, Boston, 483 Beacon St
 L F Johnson, Brookline, Longwood Towers
 C J Kickham, Brookline Office, Boston, 508 Commonwealth Ave
 C J E Kickham, Jamaica Plain Office, Brookline, 1101 Beacon St, E C
 D L Lionberger, Dedham, 709 East St
 D S Luce, Canton, 553 Washington St, P R C
 C M Lydon, Dorchester, 276 Bowdoin St
 D L Lynch, Roslindale, 61 Penfield St
 T F P Lyons, Milton Office, Boston, 270 Commonwealth Ave
 F P McCarthy, Milton Office, Boston, 371 Commonwealth Ave
 H L McCarthy, Brookline Office, Boston, 479 Beacon St
 R T Monroe, Brookline Office, Boston, 270 Commonwealth Ave
 F J Moran, Dedham, 395 Washington St
 H R Morrison, Brookline Office, Boston, 370 Marlboro St
 Hyman Morrison, Brookline Office, Boston, 483 Beacon St.
 D J Mullane, Brookline, 1101 Beacon St
 H A Novack, Brookline Office, Boston, 471 Commonwealth Ave
 J J O'Connell, Dorchester, 1061 Dorchester Ave
 E E O'Neil, Brookline Office, Boston, 270 Commonwealth Ave
 R S Palmer, Brookline Office, Boston, 330 Dartmouth St.
 G W Papen, Brookline Office, Boston, 31 Milk St.
 H C Petterson, West Roxbury Office, Boston, 29 Bay State Rd
 S H Proger, Brookline Office, Boston, 30 Bennet St.
 H A Rice, Canton, 472 Washington St.
 S A Robins, Boston, 636 Beacon St
 D D Scannell, Jamaica Plain Office, Boston, 475 Commonwealth Ave
 J A Seth, Milton Office, Boston, 47 Bay State Rd
 L A Sieracki, Norwood, 71 Winter St
 S L Skvirsky, Brighton Office, Boston, 545 State House, Leg C
 E C Smith, Brookline Office, Boston, 520 Commonwealth Ave
 Kathleen S Snow, Jamaica Plain Office, Boston, 466 Commonwealth Ave
 J W Spellman, Chestnut Hill Office, Brookline, 1101 Beacon St.
 A R Stagg, Medfield, 25 Pleasant St.
 Benjamin Tenney, Jr., Brookline, 1101 Beacon St.
 W J Walton, Dorchester, 106 Bowdoin St
 N A Welch, West Roxbury Office, Boston, 520 Commonwealth Ave, Ass't Treas
 W A White, Jr., Milton Office, Boston, 270 Commonwealth Ave
 G F Wilkins, Brookline Office, Boston, 245 State St
 P R Withington, Milton, 350 Randolph Ave
 Marjorie Woodman, Jamaica Plain Office, Boston, 21 Bay State Rd
 E T Wyman, Brookline Office, Boston, 319 Longwood Ave

Norfolk South

E B Fitzgerald, Wollaston, 563 Furnace Brook Parkway, V P
 D J Bailey, Weymouth, 165 Washington St
 F A Bartlett, Wollaston, 308 Beale St
 D L Belding, Hingham Office, Boston, 80 East Concord St, Leg C
 Harry Braverman, Quincy, 43 School St.
 R L Cook, Quincy, 1245 Hancock St, E C
 F W Crawford, Holbrook, 98 North Franklin St.
 W R Helfrich, Quincy, 17 Whitney Rd, A E C, A M N C
 Frederick Hinchliffe, Cohasset, 117 South Main St.
 E K Jenkins, So Braintree, Norfolk County Hosp, Sec
 N R Pillsbury, So Braintree, Norfolk County Hosp, M N C
 D B Reardon, Quincy, 1186 Hancock St, Ex Pres
 H A Robinson, Hingham, 205 North St, P R C

Plymouth

Mildred L Ryan, Brockton, 57 West Elm St, V P
 J C Angle, Bryantville, School St, A M N C
 Samuel Gale, Brockton, The Checkerton, Sec
 H H Hamilton, Plymouth, 70 Court St, Leg C
 A L Hurlburt, East Bridgewater, 81 Central St, A E C
 P H Leavitt, Brockton, 129 W Elm St, M N C
 D A Martin, Hanson
 C D McCann, Brockton, 12 Cottage St, P R C, E C
 J A McLaughlin, Marshfield Office, Plymouth, 17 Leyden St
 G A Moore, Brockton, 167 Newbury St
 E L Perry, Middleboro, 39 Oak St
 R E Swenson, Plymouth, 1 Carver St

Suffolk

A J A Campbell, Brighton Office, Boston, 520 Commonwealth Ave, V P
 H L Albright, Boston, 412 Beacon St.
 A W Allen, Boston, 266 Beacon St, President.
 T J Anglem, Brookline, 1180 Beacon St
 M D Altschule, Boston, 330 Brookline Ave
 F G Balch, Jr., Brookline, 1180 Beacon St, C
 J W Bartol, Boston, 1 Chestnut St, Ex-Pres
 C H Bradford, Boston, 520 Beacon St
 W J Brickley, Boston, 524 Commonwealth Ave
 W E Browne, Boston, 587 Beacon St, Leg C, A E C
 A M Butler, Boston, Mass General Hospital
 E M Chapman, Boston, 266 Beacon St
 M Henry Clifford, Boston, 501 Boylston St
 J F Collins, Revere, 123 Bennington St
 A P Der Hagopian, Chelsea, 39 Cary Ave
 N W Faxon, Boston, Mass General Hospital
 Reginald Fitz, Boston, 319 Longwood Ave, Ex-Pres
 Maurice Fremont-Smith, Boston, 12 Hereford St
 Channing Frothingham, Boston, 101 Bay State Rd, Ex-Pres
 Joseph Garland, Brookline Office, Boston, 8 Fenway
 G L Gately, East Boston, 624 Bennington St, P R C
 R L Goodale, Cambridge Office, Boston, 330 Dartmouth St
 A A Hornor, Brookline Office, Boston, 319 Longwood Ave, Vice-President.
 L M Hurxthal, West Newton Office, Boston, 600 Commonwealth Ave
 C S Keefer, Boston, 65 East Newton St, C
 H A Kelly, Winthrop, 200 Pleasant St, E C
 H E Kennard, Brookline, 1180 Beacon St
 F H Lahey, Boston, 605 Commonwealth Ave
 T H Lanman, Chestnut Hill Office, Boston, 300 Longwood Ave
 R I Lee, Boston, 264 Beacon St, Ex-Pres
 C C Lund, Boston, 20 Gloucester St, A M N C
 C F Maraldi, Boston, 276 Commonwealth Ave
 H C Marble, Newton Centre Office, Boston, 270 Commonwealth Ave, C
 L S McKittrick, Brookline, 1180 Beacon St, President Elect.
 W J Mixer, Chestnut Hill Office, Boston, 319 Longwood Ave
 Donald Munro, Boston, 818 Harrison Ave
 H L Musgrave, Revere, 620 Beach St.

F R Ober, Boston, 234 Marlboro St., C, Ex-Pres
 F W O'Brien, Boston, 475 Beacon St
 J P O'Hare, Chestnut Hill Office, Boston, 520 Commonwealth Ave
 L E Parkins, Brookline Office, Boston, 12 Bay State Rd
 L E Phaneuf, Boston, 270 Commonwealth Ave
 Helen S Pittman, Boston, 264 Beacon St
 J J Regan, South Boston Office, Boston, 520 Commonwealth Ave
 W H Robey, Boston, 202 Commonwealth Ave., Ex-Pres
 Horatio Rogers, Boston, 264 Beacon St., C
 H F Root, Brookline Office, Boston, 81 Bay State Rd
 C G Shedd, Wellesley Office, Boston 422 Beacon St., Sec
 R. M. Smith, Boston, 330 Dartmouth St., C
 C M Stearns, Chelsea, 116 Hawthorne St.
 Conrad Wesselhoeft, Boston, 315 Marlboro St., M N C
 C F Wilinsky, Boston, 330 Brookline Ave

Worcester

B C Wheeler, Worcester, 27 Elm St., V P
 A W Atwood, Worcester, 390 Main St
 George Ballantyne, Worcester, 27 Elm St., A M N C
 Jacob Brem, Worcester, 796 Pleasant St
 J B Butts, Worcester, 24 Franklin St., Leg C
 J T B Carmody, Worcester, 340 Main St
 F B Carr, Worcester, 27 Elm St., M N C
 E J Crane, Holden, Armington Lane
 Paul Dufault, Rutland, Rutland State Sanatorium
 G R Dunlop, Worcester, 27 Elm St.
 W J Elliott, Worcester, 119 Belmont St
 John Fallon, Worcester, 10 Institute Rd., E C
 L M Felton, Worcester, 36 Pleasant St.
 Donald Hight, Worcester, 27 Elm St., Sec
 Thomas Hunter, Shrewsbury, 545 Main St
 H L Kirkendall, Worcester, 27 Elm St
 D G Ljungberg, Worcester, 36 Pleasant St
 J A Lundy, Worcester, 16 Norwich St
 J C McCann, Worcester, 390 Main St.
 D K McClusky, Worcester, 7 Hawthorne St.
 J W McKeon, Worcester, 36 Pleasant St.
 J M Olson, Westboro, 54 West Main St
 F A O'Toole, Clinton, 101 Chestnut St
 E L Richmond, Worcester, 390 Main St
 N S Searcello, Worcester, 1 Selden St., A E C, P R C
 J J Tegelberg, Worcester, 390 Main St
 R J Ward, Worcester, 9 Bellevue St., C

Worcester North

E A Adams, Fitchburg, 44 Oliver St., V P
 J J Curley, Leominster, 89 West St., E C, M N C
 K J Jolma, Gardner, 86 Jonathan St
 G P Keaveny, Fitchburg, 62 Fox St., A E C
 J P Marnane, Gardner, 4 Comee St., Leg C
 J V McHugh, Leominster, 55 West St., P R C
 C S McPeak, Fitchburg, 18 Hartwell St., A M N C
 J G Simmons, Fitchburg, 30 Murtle Ave., Sec

The initials *E C* following the name of a Councilor indicate that he is a member of the Executive Committee and *A E C* that he is an alternate member of the Executive Committee. *M N C* that he is a member of the Committee on Nominations and *A M N C* that he is an alternate member of the Committee on Nominations. *Leg C* that he is a member of the Committee on Legislation. *P R C* that he is a member of the Committee on Public Relations. *V P* that a member is a councilor by virtue of his office as president of a district society and so vice-president of the general society. *C* by virtue of his office as chairman of a standing committee, *Sec* by virtue of his office as secretary of a district society and *Ex Pres* by virtue of being a past president

CENSORS FOR 1949-1950

Barnstable

D E Higgins, Cotuit, *supervisor*
 D H Hicbert, Provincetown
 Joseph N Kelly, Orleans
 O S Simpson, Centerville
 T A Wiswall, Falmouth

Berkshire

C T Leslie, Pittsfield, *supervisor*
 M A Gangemi, North Adams
 H G Mellen, Pittsfield
 T H Nelligan, Pittsfield
 G S Wickham, Lee

Bristol North

J L Murphy, Taunton, *supervisor*
 J N Brewster, Attleboro
 C B Kingsbury, Taunton
 A J Leddy, Taunton
 H G Vaughn, Attleboro

Bristol South

C C Persons, New Bedford, *supervisor*
 Herschel Heinz, New Bedford
 W F MacKnight, Fall River
 E A McCarthy, Fall River
 E L Merritt, Fall River

Essex North

L C Peirce, Newburyport, *supervisor*
 J M Barry, Lawrence
 A B Consentino, Haverhill
 W G Thompson, Andover
 P E Zanfagna, Lawrence

Essex South

S N Gardner, Salem, *supervisor*
 W R Irving, Gloucester
 C A Palladino, Lynn
 E D Reynolds, Danvers
 J R Shaughnessy, Salem

Franklin

J E Moran, Greenfield, *supervisor*
 F J Barnard, Greenfield
 J P Collieran, South Deerfield
 H A Rys, Turners Falls
 E C Thorn, Greenfield

Hampden

John Pallo, Westfield, *supervisor*
 E W Beauchamp, Springfield
 A A Palermo, Springfield
 L A Putnam, Holyoke
 J L Smead, Springfield

Hampshire

L B Pond, Easthampton, *supervisor*
 Stephen Brown, Northampton
 M E Cooney, Northampton
 T F Corriden, Northampton
 J E Hayes, Northampton

Middlesex East

T P Devlin, Stoneham, *supervisor*
 C R Baisley, Reading
 H A Bouve, Wakefield
 R E Miltzer, Woburn
 S H Moses, Winchester

Middlesex North

L F King, Lowell, *supervisor*
 Harry Black, Lowell
 C L Brennan, Lowell
 G E Carriel, Lowell
 E H Latham, Lowell

Middlesex South

H J Crumb, Lexington, *supervisor*
 W O Blanchard, Newton
 H K Bloom, Everett
 E A Gaston, Framingham
 Dudley Merrill, Cambridge

Norfolk

K S Snow, Boston, *supervisor*
 G L Doherty, Boston
 I R Jankelson, Boston
 W C Moloney, Boston
 H A Novack, Brookline

Norfolk South

F A Bartlett, Wollaston, *supervisor*
 Arthur Rapoport, Quincy
 H S Reid, Cohasset
 R E Ross, Braintree
 W L Sargent, Quincy

Plymouth

R E Swenson, Plymouth, *supervisor*
 G L Fuller, Brockton
 S E Peterson, Brockton
 R F Welch, Brockton
 E E Wiesner, Brockton

Suffolk

L M Hurxthal, Boston, *supervisor*
 T J Anglem, Boston
 J F Collins, Revere
 R L Goodale, Boston
 J J Todd, Boston

Worcester

J W McKeon, Worcester, *supervisor*
 E J Croce, Worcester
 Thomas Hunter, Shrewsbury
 H L Kirkendall, Worcester
 E L Richmond, Worcester

Worcester North

K J Jolma, Gardner, *supervisor*
 F X Dufault, Athol
 E R Pickwick, Fitchburg
 F R Pierce, Gardner
 C A Wheeler, Leominster

Essex South — Thomas B Rafferty, Lynn
 Franklin — Kenneth Jacobus, Turners Falls
 Hampden — George D Henderson, Holyoke
 Hampshire — Robert C Byrne, Hatfield
 Middlesex East — George R Murphy, Melrose
 Middlesex North — Leonard C Dursthoff, Lowell
 Middlesex South — Horace P Stevens, Cambridge
 Norfolk — David D Scannell, Boston
 Norfolk South — George D Dalton, Quincy
 Plymouth — Arthur W Carr, Bridgewater
 Suffolk — Charles H Bradford, Boston
 Worcester — A Wilson Atwood, Worcester
 Worcester North — Donald B Cheetham, Athol

OFFICERS OF THE SECTIONS FOR 1949-1950**Psychiatry and Neurology**

Chairman, Walter E Barton, Dorchester, *secretary*,
 Augustus S Rose, Belmont

Ophthalmology and Otolaryngology

Chairman, James J Regan, South Boston, *secretary*,
 Lawrence R Dame, Greenfield

Industrial Health

Chairman, Daniel L Lynch, Roslindale, *secretary*,
 Albert O Seeler, Waban

Pathology

Chairman, Donald A Nickerson, Melrose, *secretary*,
 Stanley L Robbins, Brookline

Obstetrics and Gynecology

Chairman, Daniel J McSweeney, Milton, *vice-chairman*,
 Duncan E Reid, Boston, *secretary*, Arthur
 J Gorman, Newton

Radiology

Chairman, Laurence L Robbins, Winchester, *secretary*,
 Magnus I Smedal, Waban

Dermatology and Syphilology

Chairman, Maurice M Tolman, Chelsea, *secretary*,
 John Adams, Jr, Roxbury

Physical Medicine

Chairman, Sidney Licht, Cambridge, *secretary*, Arthur
 L Watkins, Arlington

Surgery

Chairman, Franklin G Baleh, Jr, Chestnut Hill, *secretary*,
 J Hartwell Harrison, Brookline
Executive Committee — George R Dunlop, Worcester

Medicine

Chairman, Allen S Johnson, Longmeadow, *vice-chairman*,
 James A Halsted, Dedham, *secretary*, Frank
 B Carr, Worcester

Pediatrics

Chairman, Stewart H Clifford, Brookline, *secretary*,
 Gerald N Hoeffel, Boston

Anesthesiology

Chairman, Jacob Fine, Beverly, *secretary*, Leo V Hand,
 Newton Highlands

VICE-PRESIDENTS OF THE MASSACHUSETTS MEDICAL SOCIETY (Ex-Officio) FOR 1949-1950**PRESIDENTS OF DISTRICT MEDICAL SOCIETIES**

(Arranged according to seniority of fellowship in the Massachusetts Medical Society)

Middlesex North — Harry R Coburn, Lowell
 Berkshire — Norman B McWilliams, Williamstown
 Hampden — Arthur H Riordan, Indian Orchard
 Middlesex East — Ira W Richardson, Wakefield
 Norfolk South — Edmund B Fitzgerald, Wollaston
 Norfolk — W Richard Ohler, Boston
 Worcester North — Edward A Adams, Fitchburg
 Essex North — Z William Colson, Lawrence
 Bristol South — John S C Fielden, Fall River
 Essex South — Charles F Twomey, Lynn
 Bristol North — James H Brewster, Attleboro
 Suffolk — Alexander J A Campbell, Boston
 Franklin — Lawrence R Dame, Greenfield
 Plymouth — Mildred Ryan, Brockton
 Worcester — Bancroft C Wheeler, Worcester
 Middlesex South — James Marvin Baty, Belmont
 Hampshire — Edward J Manwell, Northampton
 Barnstable — Arthur J D'Eha, Harwichport

COMMISSIONERS OF TRIAL FOR 1949-1950

Barnstable — Frank O Cass, Provincetown
 Berkshire — James W Bunce, North Adams
 Bristol North — John W Cook, Mansfield
 Bristol South — Arthur C Lewis, Fall River
 Essex North — Harry H Nevers, Lawrence

OFFICERS OF THE DISTRICT MEDICAL SOCIETIES FOR 1949-1950

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vice-president, Frank Travers, Barnstable, *secretary*, Sheldon
 L Hunt, Yarmouthport, *treasurer*, John O Niles, Oyster

ville, librarian, Carroll H Keene, Cbatham, *executive councilor*, Harold F Rowley, Harwichport, *public relations councilor*, Harold F Rowley, Harwichport *legislative councilor*, Julius G Kelley, Pocasset

Berkshire — *President*, Norman B McWilliams, Williamstown, *vice-president*, Clement F Kernan, Pittsfield, *secretary*, Daniel N Beers, Pittsfield, *treasurer*, Theodore W Jones, Pittsfield *public relations councilor*, Patrick J Sullivan, Dalton *executive councilor*, Helen M Scoville, Pittsfield *legislative councilor*, Modestino Criscitello, Pittsfield

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Bristol South — *President*, John S C Fielden Jr, Fall River, *vice-president*, Joseph P Ponte Jr, *secretary and treasurer*, James E Fell, Fall River *executive councilor*, Curtis C Tripp, New Bedford, *public relations councilor*, Milton T MacDonald, New Bedford *legislative councilor*, Daniel F Gallery, Fall River

Essex North — *President*, Z William Colson, Lawrence, *vice-president*, Frederick C Atkinson, North Andover *secretary*, Harold R Kurth, Lawrence *treasurer*, J LeRoy Wood, Lawrence *librarian*, Max D Bier, Lawrence *executive councilor*, Arnold P George, Haverhill, *public relations councilor*, Harold R Kurth, Lawrence, *legislative councilor*, John T Batal, Lawrence

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Middlesex East — *President*, Ira W Richardson, Wakefield, *vice-president*, Kenneth L MacLachlan, Melrose,

secretary, Roy W Layton, Melrose *treasurer*, Charles W DeWolf, Wakefield, *librarian*, Angelo L Maietta, Winchester *executive councilor*, Thomas P Devlin, Stoneham, *public relations councilor*, Milton J Quinn, Winchester, *legislative councilor*, Justin L Anderson, Reading

Middlesex North — *President*, Harry R Coburn, Lowell, *vice-president*, Augustine Conroy, Lowell *secretary*, Philip G Berman, Lowell, *treasurer*, Mason D Brvant, Lowell *executive councilor*, William M Collins, Lowell *public relations councilor*, Samuel A Dibbins, Lowell *legislative councilor*, Joseph D Sweeney, Lowell

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Worcester North — *President*, Edward A Adams, Fitchburg, *vice-president*, Antonio D Delisle, Fitchburg, *secretary*, James G Simmons, Fitchburg *treasurer*, Frederick H Thompson, Jr, Fitchburg, *executive councilor*, John J Curley, Leominster, *public relations councilor*, James V McHugh, Leominster, *legislative councilor*, Joseph P Marnane, Gardner

ADMISSIONS RECORDED FROM MAY 22, 1948, TO MAY 23 1949

YEAR OF ADMISSION	NAME AND RESIDENCE	MEDICAL SCHOOL
1949	Ahern John Francis, Dorchester	College of Physicians and Surgeons Boston
1949	Alfano, Louis F, Melrose	Tufts
1948	Allen Henry Freeman, Boston	Harvard
1949	Ambrosino Joseph, Brockton	Middlesex
1948	Anderson Richard W, Georgetown	University of Minnesota
1948	Annunziata, Joseph Ferdinand Hopkinton	Midwest Medical College
1949	Arent, Anthony M, Cambridge	Tufts
1949	Ashe, Allan M, West Springfield	College of Physicians and Surgeons Boston
1948	Audin Francis J, Newton Highlands	University of Buffalo
1949	Bain Mary Daly, Methuen	Tufts
1948	Baker Wallace J, Willmamssett	Middlesex

1948	Bandler, Bernard, Cambridge	Columbia
1949	Barkin, Robert E., Brookline	Tufts
1948	Barnum, Francis G., Jr., Brookline	Harvard
1949	Bartels, Carl Crittenden, Saugus	Northwestern
1949	Bell, John William, Watertown	Northwestern
1948	Bennett, John Wesley, Northfield	Temple University
1949	Benton, Fred W., Needham	Boston University
1949	Berman, Carroll Z., Brockton	Chicago Medical School
1949	Bick, Malcolm W., Springfield	Harvard
1949	Bigelow, Frederick Shattuck, Concord	Harvard
1949	Bird, Lee C., North Grafton	University of Wisconsin
1948	Bixon, Alvin M., Brookline	Tufts
1948	Black, Melvin B., Brookline	Harvard
1949	Blunt, James William, Brockton	Boston University
1949	Bojar, Samuel, Brookline	Johns Hopkins University
1948	Bonner, Charles D., Boston	Boston University
1948	Bonner, Francis J., Boston	Boston University
1948	Bonner, Joseph N., Chestnut Hill	Georgetown
1948	Bonnet, Philip D., Boston	Harvard
1949	Bookstein, Jacob, Roxbury	College of Physicians and Surgeons, Boston
1949	Bouchard, Germain J., Lowell	Laval University
1948	Boyle, Jeremiah Joseph, Jr., Cambridge	Tufts
1949	Boyle, Joseph T., Barnstable	Kansas City University of Physicians and Surgeons
1949	Branchforte, John T., Bondsville	Middlesex
1949	Brennan, Robert J., Arlington	Boston University
1949	Brodie, Sidney, Brookline	George Washington University
1949	Brodsky, Erwin, Beverly	Middlesex
1948	Brown, Bruce Row, Framingham Center	Tufts
1948	Brown, Donald E., Beverly	Harvard
1949	Brown, George R., Jr., Wellfleet	Temple University
1949	Bueno, Marcio M., Fall River	University of Brazil
1948	Butler, Philip S., Worcester	Tufts
1949	Cafarella, Joseph L., Worcester	Tufts
1949	Calitri, Joseph C., Methuen	Middlesex
1948	Caplan, Sheldon M., New Bedford	Middlesex
1948	Carpinella, Charles J., Brockton	Middlesex
1948	Casale, Walter, Worcester	Long Island College of Medicine
1948	Cavalieri, Dominic, Somerville	Middlesex
1948	Centner, Paul Joseph, Malden	University of Cincinnati
1948	Chandler, Charles F., Sterling Junction	Harvard
1949	Chasen, Mignon C., Dorchester	University of Palermo
1949	Chassell, Joseph O., Stockbridge	University of Rochester
1949	Cherkas, Benjamin, Cambridge	Middlesex
1948	Cobb, Stanley, Fort Devens	Harvard
1949	Collins, Frank L., Jr., Ipswich	Tufts
1948	Colpoys, William P., Dorchester	Boston University
1948	Converse, J. Gerard, Milton	Tufts
1948	Corcoran, George Bartlett, Jr., Springfield	Yale
1948	Cordaro, Vincent F., Brockton	College of Physicians and Surgeons, Boston
1948	Corey, David Roy, Cohituate	Middlesex
1948	Crane, Chilton, Brookline	Harvard
1949	Crane, Emily T., Belmont	Cornell
1949	Cranley, John Joseph, Jr., Medford	Columbia
1948	Crosby, Ray Campbell, Framingham	Tufts
1949	Cross, James E., Southbridge	University of Rochester
1949	Curran, John F., Jr., Worcester	Tufts
1948	Curtiss, Constance, Wayland	Western Reserve University
1949	Davis, Lloyd H., Webster	Northwestern
1948	Davis, Saul P., Brockton	Middlesex
1948	Dawson, George A., Methuen	McGill University
1949	DeFeo, Joseph A., East Bridgewater	Middlesex
1949	DeLorme, Thomas L., Milton	New York University
1948	DeLuca, Marie A., Framingham	Kansas City University of Physicians and Surgeons
1948	DeNicolais, Edward J., Framingham	Middlesex
1948	DesChenes, Albert A., Fitchburg	Boston University
1948	DeStefano, Francis T., Mansfield	Middlesex
1948	Diamond, Bernard, Shawsheen	University of Edinburgh
1949	DiGiacomo, Charles, South Boston	Middlesex
1949	DiMatteo, Anthony P., Worcester	New York Medical College
1949	DiStefano, Anthony J., Shrewsbury	Marquette University School of Medicine
1949	Dodge, George Augustus, II, Brookline	Tufts
1948	Donovan, James M., Lynn	Georgetown University
1949	Donovan, John H., Waltham	Middlesex
1949	Drosdik, Vincent A., Watertown	Middlesex
1949	Duncan, Thomas F., Dorchester	Tufts
1948	Echlov, Theodore G., Brookline	Middlesex
1948	Edelstein, Joseph Melvin, Northampton	Tufts
1949	Elliott, John Richard, Canaan, Conn	Boston University
1949	Enos, Allen W., Hanover	Middlesex
1948	Entin, Moses Jacob, Quincy	Middlesex
1948	Eramo, Lincoln, Pittsfield	Tufts
1949	Etsten, Benjamin, Milton	University of St. Andrews, Scotland

1949	Evans, Richard R., Boston	Albany Medical College
1948	Evre, John D., Jr., Chestnut Hill	Columbia University
1949	Faher, Robert J., Winchester	Tufts
1948	Feingold, Myer, Malden	Middlesex
1949	Field, John A., New York	Columbia University
1949	Finlayson, Malcolm, Dorchester	Rush Medical College
1949	Finn, John J., Jr., Rutland	Tufts
1948	Finnerty, Edmund F., Jr., Waban	Tufts
1948	Florentino, Domenic S., Marlboro	Middlesex
1948	Fisher, Russell S., West Newton	Medical College of Virginia
1949	Flaherty, James R., Palmer	Tufts
1949	Flynn, Newell N., Jr., Danvers	Tufts
1949	Foley, John J., Lakeville	Georgetown University
1949	Foley, Robert E., Waltham	Cornell University
1948	Forsham, Peter H., Boston	Harvard
1949	Foster, Augusta A., Cambridge	Tufts
1948	Franseen, Elmer F., Boston	Harvard
1948	Freedman, Jacob J., Lawrence	Middlesex
1949	Freis, Edward David, Winthrop	Columbia University
1948	Fried, Marcus B., Springfield	Kansas City University of Physicians and Surgeons
1949	Fulchino, Harry L., Revere	Tufts
1948	Funkenstein, Dan H., Boston	Tulane University
1949	Gaudreau, Robert C., Fairhaven	Middlesex
1948	Gelinas, Joseph A., Fitchburg	Laval University, Quebec
1949	Gettings, Carroll P., Fall River	Tufts
1949	Giansiracusa, Joseph E., Belmont	University of California Medical School
1949	Gill, Merton M., Stockbridge	University of Chicago
1948	Gold, Sol M., Hallowe	Middlesex
1948	Goldberg, Jack Jacob, Brookline	College of Physicians and Surgeons, Boston
1949	Goldman, Robert H., Leominster	Kansas City University of Physicians and Surgeons
1949	Goldman, Sidney, Fitchburg	Middlesex
1949	Golub, Benjamin S., Rochester	Boston University
1948	Goodhue, Frederick W., South Hanson	Tufts
1948	Gould, Henry, Natick	Kansas City University of Physicians and Surgeons
1948	Gowder, John Frederic, Pittsfield	University of Vermont
1949	Grande, Gaetano G., East Boston	Middlesex
1948	Gray, Seymour J., Brookline	University of Pennsylvania
1949	Greene, Thomas F., Dorchester	Tufts
1949	Greenstein, Samuel S., Lowell	Middlesex
1948	Grenn, Francis P., New Bedford	Middlesex
1948	Grewal, Jogindar S., Westfield	Boston University
1949	Grier, James R. S., New Mexico	Harvard
1949	Griesemer, Robert D., Boston	Harvard
1949	Gross, Harold A., Springfield	New York University
1948	Guernieri, Antonio George, Stockbridge	Marquette University
1948	Gutman, Murray, Wellesley	Chicago Medical School
1948	Habhab, Homode J., Bradford	Middlesex
1949	Hackworth, Lorye E., Waltham	Harvard
1948	Hagler, Sumner, Kennerma	Columbia University
1949	Haidak, Gerald L., Hinsdale	Chicago Medical School
1949	Hamilton, George H., Jr., North Andover	Tufts
1949	Hanna, George A., Jr., Malden	Wayne University
1948	Harmon, Sidney Hyman, Cambridge	College of Physicians and Surgeons, Boston
1948	Hassett, Arthur J., Jr., Weymouth	Tufts
1949	Hazard, Sprague W., Foxboro	Columbia University
1949	Heath, Parker, Winchester	University of Michigan
1948	Heffernon, Elmer W., Boston	Tufts
1948	Hennell, Thomas P., Pittsfield	Columbia University
1948	Hickey, William F., Jr., Winchester	Harvard
1948	Hicks, Samuel P., Chestnut Hill	University of Pennsylvania
1948	Hill, Robert Clayton, Roxbury	Hahnemann Medical College
1949	Hinman, Crawford H., Boston	Harvard
1949	Hirsch, Frank A., Methuen	Middlesex
1948	Hoffman, William, Lynn	Middlesex
1948	Holtzman, Saul C., Bedford	Boston University
1949	Howard, Malcolm M., Greenfield	Long Island College of Medicine
1948	Howe, Calderon, Jamaica Plain	Harvard
1949	Hubbard, Edward O., Jr., Providence, R. I.	Tufts
1948	Hughes, Wilson E., Fall River	Yale
1948	Hurley, Melvin Timothy, Newton Center	Stanford University
1948	Jacobs, Eli I., Belmont	Middlesex
1949	Jacobs, Nathan, Fisherville	Middlesex
1948	Jacobs, Edward L. G., North Easton	Middlesex
1948	Jagoda, Leonard S., East Longmeadow	Creighton University
1949	Jansen, Alfred W., Norwood	Tufts
1948	Jeffries, William M., Boston	University of Virginia
1949	Jewett, John F., Boston	Harvard
1949	Jillson, Otis F., Boston	Tufts
1949	Joffe, Ellis, Hallowe	University of Brussels
1949	Johnson, Leonard A., Lawrence	Middlesex
1949	Johnson, Verner S., Hopedale	University of Nebraska
1948	Jones, William N., Boston	University of Chicago

1949	Kaess, Kenneth Richard, Brookline	Harvard
1949	Kagan, David B., Pittsfield	Chicago Medical School
1948	Kahn, Walter, Chelmsford	University of Bonn
1949	Kanowitz, Sidney, Springfield	Middlesex
1948	Kanter, Stanley Samuel, Arlington	Washington University
1948	Kaplan, Morris, Bridgewater	College of Physicians and Surgeons, Boston
1949	Kaplan, Samuel, Newton Highlands	Long Island College of Medicine
1948	Kaufman, Alan L., New Bedford	Middlesex
1948	Kaye, Maxwell E., Canton	Midwest Medical College
1948	Keigan, Archie Graham, East Braintree	Tufts
1948	Keller, Maurice J., Salem	Columbia University
1948	Kennedy, William E., Fall River	Yale
1948	Kenworthy, Roger A., Boston	University of Vermont
1948	Kerhulas, Andrew A., Cambridge	Duke University
1949	Kernan, Reginald D., Milton	Harvard
1948	Kerr, Richard Carpenter, Newton	Harvard
1949	Kilfoyle, Richard M., Dorchester	Tufts
1949	Kilroy, Edward F., Worcester	Harvard
1949	King, Joseph A., Jr., Worcester	New York Medical College
1948	Kingsland, Lawrence E., Hingham	Harvard
1948	Klibanoff, Samuel, Springfield	Harvard
1948	Kligerman, Sidney, Boston	University of Illinois
1948	Knapp, Peter Hobart	Harvard
1948	Knight, Robert Palmer, Stockbridge	Northwestern
1948	Kohn, Kurt Heinz, Easthampton	State Medical School, Vinnitza
1949	Konefal, Stanley H., Medford	Boston University
1949	Kramer, Philip, Boston	University of Chicago
1949	Kraus, Edward I., Springfield	Hahnemann Medical School
1948	Kunian, Louis, Salem	Middlesex
1948	Kvitka, Laurence, Brookline	Middlesex
1948	Land, William, Salem Depot, N. H.	Boston University
1949	Lane, Marvin K., Holliston	Middlesex
1949	Lappin, Sidney H., Brighton	Middlesex
1949	Lemon, Henry M., Quincy	Harvard
1949	Levitz, Edward R., Holyoke	Middlesex
1949	Licata, Daniel D., Wakefield	Middlesex
1948	Litter, Julius, Brighton	Boston University
1948	Lorentz, John J., Methuen	Georgetown
1948	Luongo, Michael A., East Boston	Boston University
1949	Lynch, William Albert, West Newton	Tufts
1948	MacDonald, Alexander S., Beverly Farms	Cornell
1948	MacGilpin, Harold H., Jr., Worcester	University of Pennsylvania
1948	Mackler, Edward D., New Bedford	Tufts
1948	MacMillan, Robert J., Newton	University of Cincinnati
1948	Malmquist, Carl Y., Jr., Worcester	Yale
1948	Mann, Bernard Freeman, Jr., Westwood	Boston University
1948	Martin, William J., Worcester	New York Medical College
1949	Mason, Andrew V., Bridgewater	Tufts
1949	McCready, Frederick J., Worcester	Tufts
1949	McGoldrick, Louis G., Worcester	Tufts
1948	McGovern, Richard H., Lawrence	Middlesex
1949	McGrath, Edward F., Milton	University of Pennsylvania
1949	McIntire, Frederic J., Jr., Marblehead	New York University
1949	McKenna, Romayne F., Fall River	Creighton University
1948	McMillan, Albert S., Agawam	University of Virginia
1949	McVey, Wilma H., Boston	Albany Medical College
1949	Merrill, John P., Winchester	Harvard
1949	Metcalf, William, Newton Center	Johns Hopkins
1948	Miles, Henry H. W., Newton	Tulane University
1948	Miller, Paul Ralph, Newton	Boston University
1948	Morrison, James M., Worcester	St. Louis University
1949	Moschella, Ralph, Pittsfield	College of Physicians and Surgeons, Boston
1949	Mulligan, John J., Bridgewater	Middlesex
1949	Murphy, Joseph F., Worcester	Tufts
1949	Murray, Joseph E., Brookline	Harvard
1949	Myerson, Ralph M., Medford	Tufts
1949	Nathans, Sydney, Chicopee Falls	Kansas City University of Physicians and Surgeons
1948	Newman, Arthur Sumner, Newton	Middlesex
1948	Nieckoski, Julian, Greenfield	Harvard
1949	Nielsen, Odd S., Hull	Boston University
1949	Norman, Paul P., Malden	Middlesex
1948	Norton, Thomas M., Pittsfield	Georgetown
1948	O'Brien, Frederick Francis, Winchester	Tufts
1949	O'Donnell, Anne R., Worcester	Tufts
1949	Ohler, Robert L., Wellesley Hills	Harvard
1948	O'Keefe, Arthur Francis, West Newton	Duke University
1949	Olson, Raymond O., Boston	Harvard
1948	O'Neill, Walter J., New Bedford	Midwest Medical College
1948	Oppenheim, Harry, Rockland	College of Physicians and Surgeons, Boston
1948	Orms, Harry W., Lynn	Wayne University
1948	Ostroger, Joseph George, Medford	Middlesex
1949	Paige, Emil, Framingham	Tufts

1949	Parker, Stanley G., Cataumet	Middlesex
1948	Parker, Sydney S., Gloucester	Middlesex
1949	Patterson, Marcel, Boston	Tulane
1948	Pearson, Carl M., Boston	Boston University
1949	Pepe, Enrico A., East Boston	Harvard
1948	Peterson, Norvell L., Boston	Kansas City University of Physicians and Surgeons
1948	Pierce, James F., Worcester	Georgetown
1948	Pitta, Carl Almeida, South Dartmouth	Kansas City University of Physicians and Surgeons
1949	Quincy, William C., Jr., Boston	Johns Hopkins
1948	Quinn, Edward J., Brookline	University of Virginia
1949	Ravin, Iver S., Brookline	Boston University
1949	Readdy, Marjorie E., South Braintree	Boston University
1948	Regan, Ellen F., Framingham	Yale
1949	Ricci, Alpine L., Malden	Middlesex
1949	Ripa, Anthony S., East Boston	Middlesex
1949	Robins, Eli, Cambridge	Harvard
1949	Robinson, Charles, Dorchester	College of Physicians and Surgeons, Boston
1949	Roe, Benson B., Boston	Harvard
1949	Rogers, Alexander S., Holyoke	Middlesex
1948	Rogers, Theodore, Dorchester	Middlesex
1949	Rosenberg, Joseph, Fitchburg	Middlesex
1948	Rosenberg, Robert, New Bedford	Middlesex
1948	Rosenman, Leonard Daniel, Newton Center	University of Michigan
1949	Rosenthal, Samuel, Cambridge	Middlesex
1949	Rostler, Alexander Erich, Fall River	University of Basel
1948	Rothman, Martin, Haverhill	Tufts
1948	Rothseid, Albert S., Methuen	Middlesex
1948	Rounseville, Wilfred V., Attleboro	Tufts
1948	Rubin, Frank Fred, Quincy	Middlesex
1949	Rubino, Bernard C., Athol	University of Vermont
1949	Rubinow, Merrill B., Framingham	Long Island College of Medicine
1949	Rurman, Herbert, Belmont	Middlesex
1948	Ryder, Brooks, Boston	Tufts
1949	Saccone, William A., Revere	Middlesex
1949	Sacks, Morris I., Revere	Middlesex
1948	Sarlo, Vincent M., New Bedford	Middlesex
1948	Saunders, Peter, Roxbury	Hungarian Royal Erzsebet University
1948	Scaringi, Joseph, West Somerville	Middlesex
1948	Schwartz, Harry, Wakefield	Middlesex
1948	Segal, Allan L., Salem	Queens University
1949	Semenza, Nicholas J., Waltham	Middlesex
1948	Shannon, Mary C., Worcester	Kansas City University of Physicians and Surgeons
1949	Shannon, Paul V., Worcester	Georgetown
1949	Shaw, Elmer A., Plymouth	Tufts
1948	Shipp, Frank Loudon, Newton Lower Falls	University of Toronto
1949	Shoul, Melvin L., Newton Center	Tufts
1948	Shub, Albert W., Lynn	Middlesex
1948	Shushan, Arthur A., Watertown	Kansas City University of Physicians and Surgeons
1949	Sikorski, Stanley S., Fairhaven	Middlesex
1949	Silliker, Stuart A., Cambridge	Tufts
1948	Simmons, Harold L., Jr., New Bedford	Boston University
1948	Singer, Peretz, South Boston	Middlesex
1949	Slivkin, Stanley E., Dorchester	Middlesex
1948	Slomkowski, Thaddeus Joseph, North Quincy	Boston University
1948	Solow, Alfred L., Sharon	Middlesex
1948	Southwick, Edward H., Lowell	Albany Medical College
1949	Souza, Dorothea L., Medford	Tufts
1948	Spangler, Arthur S., Boston	Harvard
1948	Stahler, Sidney, Sharon	New York Medical College
1948	Stanbury, John B., Cambridge	Harvard
1948	Stanley, Malcolm M., Brookline	University of Louisville
1948	Sterling, Haskell, Brookline	Middlesex
1948	Stimson, Allan B., New Bedford	Harvard
1949	Stone, Eric Percy, Framingham	Harvard
1948	Stone, Samuel M., Springfield	Middlesex
1949	Taggart, William J., Wellesley Hills	Cornell
1948	Talbot, Herbert Selian, Natick	Columbia
1948	Teitel, Milton Henry, Springfield	College of Physicians and Surgeons, Boston
1948	Thaler, Richard W., Boston	Harvard
1948	Thiery, Raymond D., Bridgewater	Harvard
1949	Thomson, Charles R., Amesbury	New York University
1949	Tolnick, Bernard, Jamaica Plain	Boston University
1948	Trafton, Marion Z., Dorchester	Boston University
1948	Valatka, Joseph A., Abington	Middlesex
1948	Varnias, Anthony D., Jr., Worcester	Boston University
1949	Varraro, Emma M., Waltham	Middlesex
1949	Wakefield, Robert D., Worcester	University of Vermont
1949	Wales, Burton L., Jr., Cambridge	Cornell
1949	Waterman, George E., Clinton	Boston University
1949	Watt, Robert Douglas, Hingham	Tufts
1949	Weinberger, Howard J., Belmont	University of California Medical School
1949	Weinsaft, Paul P., Winthrop	University of Paris
1948	Weiss, Jess B., Dorchester	Middlesex

1949	Wheelis, Allen B , Stockbridge	Columbia University
1949	Williams, David Willard, Springfield	Harvard
1948	Williamson, Charles Readv, Waban	Harvard
1948	Wilson, John L , Palo Alto, California	Harvard
1948	Winston, Murray Richard, Lexington	University of Lausanne
1949	Witkow, Alexander, Worcester	New York College of Medicine
1948	Wittenborg, Martin Herman, Framingham	Johns Hopkins
1949	Wolfson, William Q , Chicago	Middlesex
1948	Wood, Dwight Reynolds, South Weymouth	Tufts
1948	Wright, Henry Collier, Williamstown	New York University
1949	Zalon, Leo, Bridgewater	Middlesex
1948	Zambon, Leo U , Needham	Middlesex
1949	Ziolkowski, Henry John, Chicopee	Middlesex

DEATHS REPORTED FROM MAY 22, 1948, TO MAY 23, 1949

ADMITTED	NAME	PLACE OF DEATH	DATE OF DEATH	AGE
1884	†Alanson J Abbe	Winter Park, Florida	January 3, 1949	85
1903	†William H Allen	Mansfield	September, 1948	80
1928 } 1941 }	Bernard H Appel	Brighton	September 3, 1948	49
1900	Newton S Bacon	Boston	March 1, 1949	76
1927	†Florence Bailey	Lawrence	December 24, 1948	71
1925	Henry Barnes	New Bedford	May 29, 1948	71
1928	Robert B Barton	Wellesley Hills	November 30, 1948	47
1898	†Pierre Brunelle	Lowell	February 10, 1949	—
1913	Thomas F Capeles	Haverhill	August 12, 1948	64
1926	Walton G Card	Haverhill	November 11, 1948	60
1911	Henry G Carroll	Boston	August 11, 1948	64
1937	Arthur C Carter	South Dartmouth	November 26, 1948	48
1897	†Oliver W Cobb	Easthampton	April 6, 1949	90
1923	James F Condrick	Quincy	May 27, 1949	62
1900	†Samuel W Crittenden	Wakefield	March 26, 1949	91
1913	Louis W Croke	Boston	February 15, 1949	63
1912	Albert E Cross	South Carolina	November 6, 1948	76
1926	Martin F Crotty	Cambridge	June 5, 1948	34
1901	†Morton E Cummings	Malden	April 20, 1949	74
1900	†William E Currier	Leominster	November 23, 1948	47
1895	Francis P Denny	Brookline	September 10, 1948	79
1909	Kinton F Dorion	Lawrence	January 29, 1949	41
1901 } 1909 }	†Frederick L Doucett	East Weymouth	June 20, 1948	78
1942	Henry A Dunphy	Palmer	June 11, 1948	62
1905	Calvin B Faunce, Jr	Boston	September 22, 1948	66
1906	†Carrie I Felch	Boston	June 13, 1948	73
1902	†Elisha Flagg	New York	June 8, 1948	82
1936	†John K Gatsopoulos	Florida	December 20, 1948	74
1921	Charles J C Gillon	Taunton	January 15, 1949	59
1938	Nathan B Glassman	Dorchester	June, 1948	59
1911 } 1934 }	Edward J Grainger	Winthrop	July 25, 1948	70
1926 } 1942 }	Robert C Hannigen	Amesbury	December 16, 1948	71
1903 } 1933 }	William A Hare	Springfield	July 29, 1948	76
1911	John H Hartnett	Worcester	May 10, 1949	73
1929	James C Healy	Boston	November 19, 1948	46
1924	Earl K Holt	Harding	November 10, 1948	59
1907 } 1943 }	Henry L Houghton	Boston	June 14, 1948	80
1918	John Hughes	Rhode Island	February 12, 1949	66
1924	George Klein	Norwood	June 18, 1948	58
1897	†Joseph I Lindsay	Grafton	June 6, 1948	84
1897	James F Loughran	Lowell	April 17, 1949	80
1912	†Carl C MacCorison	Maine	June 4, 1948	70
1945	Howard D Mailey	California	October 14, 1948	33
1895	†Arthur W Marsh	Worcester	June 24, 1948	83
1909 } 1937 }	Lewis S McQuade	Quincy	March 10, 1949	64
1927	John M Murphy	Brockton	April 24, 1949	68
1909 } 1919 }	Abraham Myerson	Boston	September 2, 1948	67
1926	†James W O'Neil	Springfield	May 22, 1949	62
1891	†Maurice W Pearson	Ware	June 22, 1948	81
1906	†Lewis W Pease	Weymouth	March 17, 1949	73
1909 } 1929 }	William P Pratt	Quincy	August 16, 1948	71
1920	John C Roe	Pittsfield	March 11, 1949	60

1910 } 1945 }	Carl W. Rosenbloom	Holvoke	March 2, 1949	62
1946	Ernest Rosmarin	Boston	June 29, 1948	67
1919	Solomon Schwager	Pittsfield	November 30, 1948	57
1952	Jabran Y. Skeirik	Boston	December 5, 1948	56
1900	Albert E. Small	Boston	June 9, 1948	72
1917 } 1922 }	Lillian R. Smith	Harwich	April 13, 1949	63
1915	Richard P. Strong	Boston	July 4, 1948	76
1915	John A. Sullivan	Minnetonka	April 8, 1949	62
1915 } 1941 }	Arthur J. Taveira	New Bedford	June 18, 1948	60
1914	George H. Torner	Brookline	June 1, 1948	76
1915	John H. Weller	Boston	November 19, 1948	69

†Retired fellow

Total number of deaths of active fellows

45

Total number of deaths of retired fellows

18

Grand total

63

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*BENJAMIN CASTLEMAN, M.D., *Associate Editor*EDITH E. PARRIS, *Assistant Editor*

CASE 35301

PRESENTATION OF CASE

A seventy-five-year-old housewife entered the hospital with intermittent frequency, burning and hematuria.

Fourteen years before entry and again seven years later, she underwent suprapubic operations for carcinoma of the bladder, following which she was entirely well until two months before entry, when the above-mentioned symptoms developed.

Physical examination revealed a blood pressure of 110 systolic, 90 diastolic, and moderate cardiac enlargement, with a very slight, soft, apical, sys-

tolic murmur. Pelvic examination showed no fixation of the bladder base and no induration.

Examination of the blood disclosed a red-cell count of 3,160,000, with a hemoglobin of 9.7 gm, and a white-cell count of 9000. The nonprotein nitrogen was 28 mg per 100 cc. The urine had a specific gravity of 1.014 and gave a ++ test for albumin; the sediment contained an occasional white cell, rare red cells and many bacteria. A blood Hinton test was negative.

An intravenous pyelogram showed normal-appearing urinary passages on the right. There was no evidence of excretion on the left over a period of one hour. Both kidney shadows were normal in size, shape and position. The bladder shadow demonstrated lobulated filling defects of the floor and left side. The bones were slightly decalcified, but no localized areas of destruction were seen. There was a group of calcifications in the left side of the pelvis (Fig 1).

On cystoscopy two small papillary tumors of the bladder base and a questionable infiltrating tumor involving the anterior wall just above the vesical orifice were seen. Biopsies of the right and left base and the anterior wall showed no tumor. Retrograde pycelography was reported as demonstrating a small amount of filling on the left, which outlined dilated calyces with irregular margins and a large, round defect in the pelvis of the kidney. The ureter was widened and tortuous, and irregular defects were present within it. A urine culture, taken at the time of cystoscopy, grew abundant colon bacilli and nonhemolytic streptococci.

On the twelfth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR SYLVESTER B KELLEY As one glances through the history of this seventy-five-year-old woman there are a number of preliminary thoughts that run through one's mind in an attempt to find an explanation for the symptoms presented. One surmises that with a red-cell count of 3,160,000 and a hemoglobin of 9.7 gm the disease had been going on much longer than the two-month period described by the patient. Recurrent cancer in the bladder is a good possibility, freedom from symp-



FIGURE 1

toms for seven years after specific therapy for a bladder tumor is by no means indicative of a cure. The normal nonprotein nitrogen and the reasonably good specific gravity of the urine suggest that one kidney at least had fairly good function. It is unfortunate that the physical examination includes no mention of the kidneys or abdominal findings. In the majority of cases a tumor of the renal parenchyma can be felt by bimanual palpation. Similarly, another x-ray film taken twenty-four hours after the injection of the intravenous dye might have given invaluable assistance in revealing why the left kidney failed to excrete enough dye for visualization of the pelvis and calyces within the customary hour. The lobulated filling defects on the floor and left side of the bladder should be interpreted cautiously. Extravesical masses, or even an enlarged prostate in male patients, may simulate

bladder tumors. Cystoscopic biopsies are not infallible. The operator may get his specimen from the area around a tumor, or the tissue that he removes may vary greatly in its degree of malignancy from that elsewhere in the same tumor. Whatever this patient had, it apparently involved the kidney, ureter and bladder.

A history of burning, frequency and hematuria ordinarily suggests stone, tumor, tuberculosis or inflammatory reaction somewhere along the urinary tract.

First, let us consider an acute inflammatory process, not because it is the most likely but because it can be eliminated most easily. Such a condition would have caused more severe symptoms and would have been constant. The urine, furthermore, would have contained more pus cells. An infection of the urinary tract severe enough to cause gross hematuria would be manifested by a generalized inflammatory reaction in the bladder, which certainly would have been commented upon by the cystoscopist. I believe, then, that the patient had something more than a colon-bacillus infection of the urinary tract.

Tuberculosis has no respect for age, but it is distinctly less common in the urinary tracts of elderly people than in those of patients between twenty and thirty-five. Although the dilated calyces with irregular margins are consistent with renal tuberculosis, this disease should not have caused a filling defect of the renal pelvis. This degree of tuberculous involvement of a kidney, furthermore, would have been accompanied by the characteristic retraction of the ureter and gaping ureteral orifice as noted by cystoscopy. Let us eliminate tuberculosis, therefore, from the possibilities.

Calculous disease of the urinary tract merits consideration, but is a rather unlikely cause of these symptoms. The patient mentioned no pain in the side, and no calculi are mentioned in the x-ray report. A nonopaque uric acid stone in the kidney pelvis might account for the filling defect in the left kidney, but a stone there would probably have caused a more extensive generalized dilatation of the pelvis and all the calyces. A nonopaque stone blocking the lower ureter would have resulted in a uniform dilatation of the ureter above the obstruction instead of the irregular defects described in the history. In view of these considerations I believe that stones in the urinary tract do not explain the clinical picture.

This leaves cancer as the final possibility. Despite the negative biopsies I believe the patient had carcinomatous areas in her bladder. At times, I will grant that an indwelling urethral catheter chafing against the bladder mucosa may create lesions resembling bladder tumors, but here we have no mention of previous constant drainage and so I believe that we should lend credence to the views of the cystoscopist. Even in the presence of smooth, regular outlines of the kidneys, tumors of the renal

parenchyma are possible. Without the characteristic narrowing and elongation of the calyces, however, this type of renal tumor is unlikely. The generalized dilatation of the calyces and the defect in the outline of the renal pelvis are more consistent with the papillary type of carcinoma involving the kidney pelvis primarily. The tendency of these papillary tumors to metastasize down the ureter also would explain the dilatation and irregular filling defects of the ureter on the basis of secondary implants from the pelvis. Primary tumor of the ureter can produce similar filling defects, but this is a relatively uncommon disease and it probably would not be accompanied by filling defects of the kidney pelvis about it. In cases of long standing, tumors of the renal pelvis may even extend down the ureter and cause implants in the bladder mucosa. In my opinion, therefore, the history and x-ray findings in this case could all be explained satisfactorily by a papillary carcinoma of the left renal pelvis with secondary implants in the left ureter and in the bladder.

May we see the x-ray films?

DR STANLEY M WYMAN: The first three films are after intravenous examination and are normal. At the end of sixty minutes the left kidney does not appear to be appreciably larger than it was at the beginning of the examination. This suggests that the kidney is not functioning. The areas of calcification described lie in the pelvis above the bladder, slightly to the left, and I would say outside the urinary passages. The filling defect in the bladder can be seen best on the empty film. There is a large, irregular, filling defect on the left, and there is a suggestion of smaller defects about it. The last film is a retrograde examination. We have only one film, and it shows a large number of irregular, nonopaque, filling defects involving the upper third of the ureter and pelvis. The calyces seem to be wide and irregular.

DR KELLEY: This dilated lobular ureter is not quite what I had expected from the description, but I think it fairly well eliminates the possibility of tuberculosis and nonopaque stone. It looks as if something were growing from the lining of the renal pelvis out toward the calyces. Sometimes blood clots give this irregular filling of the ureter.

After viewing these x-ray films I will still adhere to my original guess of a papillary tumor primary in the renal pelvis, with secondary implants in the ureter and bladder.

DR WYLAND F LEADBETTER: I have nothing to add except that the procedures were carried out as indicated. We exposed the kidney through a left lumbar incision and found a very dilated, looped ureter, which seemed to contain tumor. The ureter was ligated just above the pelvic brim and resected with the kidney. Then through an anterior approach an extraperitoneal resection of the lower ureter with a small cone of bladder was carried out

CLINICAL DIAGNOSIS

Papillary carcinoma of left ureter, renal pelvis and bladder

DR KELLEY'S DIAGNOSIS

Papillary carcinoma of left ureter, renal pelvis and bladder

ANATOMICAL DIAGNOSES

Papillary carcinoma of renal pelvis, with extension into ureter and with metastases to ureteral mucosa

Hydronephrosis

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: As this photograph (Fig 2) shows, there is a large papillary friable tumor



FIGURE 2

involving the entire pelvis and extending into the proximal ureter. It is also evident that there are numerous mucosal metastases not only in the upper

ureter but also in the lower portion removed separately (Fig 2) Microscopically the tumor is fairly well differentiated and might be graded two (on a scale of three)

About a month later a cystoscopy showed a papillary tumor about 3.5 cm in diameter with a broad base occupying the left posterior wall behind the left ureteral region. This was resected transurethrally, and radon seeds implanted. Histologically the tumor was similar to that in the kidney and ureter. On a routine cystoscopic checkup six months later three more small papillary tumors were seen in this same region of the old ureteral orifice, which had been excised at the first operation. In addition there were now several others on the anterior and lateral walls. All these tumors were thoroughly coagulated. It was believed that cystectomy was not indicated because of the patient's age.

The question whether these tumors implant or are independent growths always arises in such a case. I personally have leaned toward the idea that many of the so-called metastases or recurrences were really new tumors produced by the same stimulus that caused the original one. In this case, however, the evidence seemed to be more in favor of implantation or recurrence.

CASE 35302

PRESENTATION OF CASE

First admission A sixty-five-year-old man entered the hospital with signs of intestinal obstruction and abdominal pain of six days' duration. A barium enema showed a filling defect in the descending colon. On the fifth hospital day a cecostomy was performed, and on the eighteenth day a freely movable segment of descending colon containing an adenocarcinoma (Grade III) was excised and an end-to-end anastomosis made between the severed ends of bowel. The tumor had penetrated the overlying serosa and extended to several regional lymph nodes. All these nodes were removed, and no distant metastases were found. The gall bladder was distended, tense and full of stones. The postoperative course was stormy. Wound sepsis developed, and when this was controlled and the cecostomy tube removed, an abscess developed under the left leaf of the diaphragm, which proved to be connected by a fistulous tract to the bowel anastomosis. A transverse colostomy was performed, and the abscess drained. Large doses of penicillin and a short course of sulfadiazine were used in conjunction with six whole-blood transfusions and one plasma transfusion during this long illness. Later, the wound had to be reopened, and another abscess in the same region was entered and drained. The patient then began to complain of calf pain, and his left leg was swollen. Bilateral ligation of the superficial femoral

veins was done. He was discharged on the sixty-fifth day after admission.

Final admission (thirteen days later) After discharge the patient felt well and was ambulatory. He increased his activities, had a good appetite and gained weight. On the day before readmission he had a sudden, severe shaking chill, following which his temperature was found to be 101°F. He complained of pain in the left chest, and had a slight cough productive of small amounts of white sputum. Later in the day there were more chills, and the patient became confused and disoriented. He was brought to the hospital thirty-six hours after the first chill.

Physical examination revealed a disoriented man. The skin was hot and dry. The scleras were icteric. The right pupil was smaller than the left, and both reacted sluggishly. The tongue was red and coated. The heart was enlarged to percussion. A Grade II systolic murmur and a diastolic gallop were heard at the apex. The percussion note over the left-lung base was dull, and the breath sounds distant. No bronchial breathing or rales were heard. The drainage wound in the left flank was healed. The colostomy site was clean. The abdomen was soft except in the right upper quadrant, where there were resistance and tenderness. Neurologic examination was negative.

The temperature was 102°F, the pulse 100, and the respirations 28. The blood pressure was 115 systolic, 60 diastolic.

Examination of the blood showed a hemoglobin of 13.7 gm per 100 cc and a white-cell count of 10,550, with 87 per cent neutrophils. The specific gravity of the urine was 1.016, and there was a ++ test for albumin and a + foam test for bile. The sediment was loaded with hyaline casts. Examination of the spinal fluid was negative. A chest film was normal. Further studies on the day after admission elicited the following information: a serum bilirubin of 2.6 mg per 100 cc direct, 3.5 mg indirect, a chloride of 88 milliequiv per liter, a carbon dioxide of 23.2 milliequiv per liter, an amylase of 38 units per 100 cc, a nonprotein nitrogen of 60 mg per 100 cc, and a total protein of 6.3 gm per 100 cc. A throat culture was negative for beta-hemolytic streptococci and pneumococci.

Thirty-six hundred units of penicillin was given intramuscularly every two hours. The night after admission the patient was comatose. Respirations were deep at 20 per minute. The temperature had fallen in a steady line to 95°F. The bladder was catheterized, but no urine was obtained. Review of the blood smear in hematologic consultation revealed no toxic granules in the neutrophils in a nearly normal count, the presence of "viral lymphocytes" was noted. Death occurred on the third hospital day.

DIFFERENTIAL DIAGNOSIS

DR VICTOR G BALBONI This sixty-five-year-old patient was first admitted to the hospital with signs of intestinal obstruction that was found to be due to cancer of the descending colon. This cancer, as well as several locally involved lymph nodes, was removed, and no distant metastases were found at the time of operation. It was noted at operation that he had cholelithiasis. The postoperative course was complicated by the development of a left subdiaphragmatic abscess, which required drainage. Presumably at the time of the operation he was transfused, and he was transfused several times again during the first hospital admission, which was a long one amounting to sixty-five days. Sometime during this first hospital admission he developed a thrombophlebitis of the left leg, and both superficial femoral veins were tied off. There was no evidence of pulmonary embolism during the first admission.

He went home, and was up and about, apparently eating well and having no symptoms, when he suddenly became acutely ill with chills, fever and pain in his chest requiring readmission to the hospital.

This episode raises the question of whether or not he could have had a pulmonary embolus. However, there was no hemoptysis, no rales were heard in the lungs, and his rapidly downhill course, with the development of jaundice and renal failure, does not suggest pulmonary embolism. Jaundice may occur with large pulmonary infarcts, but the jaundice is usually mild and does not develop for several days after the infarction. The jaundice in these cases is presumably due to the breakdown of blood in the infarcted area of the lung and almost always occurs in a patient with congestive heart failure. Clinical examination of the chest on this second entry revealed some dullness and diminished breath sounds in the left lower lung posteriorly, but these findings could be well accounted for by a high diaphragm resulting from his previous subdiaphragmatic abscess. Pulmonary embolism after both superficial femoral veins had been ligated would also be unusual. Emboli can develop proximal to the ligation of the superficial femoral veins or in the deep femoral veins, but such a course of events seems unlikely in this case.

We know that this man had cholelithiasis discovered at the time of operation, and the possibility of acute cholecystitis with obstruction of the common bile duct must be considered. The serum bilirubin was 2.6 mg per 100 cc direct and 3.5 mg indirect. In obstructive jaundice the van den Bergh reaction is primarily of the direct type, thus these readings although not very helpful suggest that the reaction was primarily indirect, indicating that the jaundice was of the type seen in primary liver-cell damage. No other liver-function tests are given. It would have been helpful if we had had a thymol

turbidity test and an alkaline phosphatase. In obstructive jaundice the alkaline phosphatase is usually elevated above the normal of 5 Bodansky units. In obstructive jaundice the thymol turbidity is usually normal (0 to 4 units), and in hepatocellular jaundice (hepatitis) the thymol turbidity is usually markedly elevated anywhere up to 30 or 35 units but rarely above 20 units. The serum amylase remains normal in both types as it was in this case.

The patient's course on the second hospital entry was rapidly downhill, with the development of jaundice, coma and renal failure.

On the basis of the evidence I must assume that the jaundice was of the intrahepatic type seen when the liver is severely damaged. Miliary metastases to the liver from the original carcinoma of the colon could produce this picture, as also could multiple metastatic abscesses of the liver. I see no way of completely ruling out these possibilities. The white-cell count was not very abnormal being only 10,500, with 87 per cent neutrophils, and is against pyogenic abscesses of the liver. If there were multiple metastases in the liver, it is reasonable to assume that they would have been recognized at the time of the operation.

None of the diagnoses so far mentioned seem to explain adequately the rapidly downhill course that this patient showed, with clinical evidence of hepatic and renal failure. With severe hepatic failure coma is quite common, and renal failure may occur. The exact cause of the renal failure in severe liver disease is not clearly understood, but it is known that a type of nephrosis may develop. We know that this man had a transfusion at the time of his operation for cancer of the bowel, seventy-eight days prior to the development of the jaundice and that he had several other transfusions during his first hospital stay. Hepatitis of the so-called homologous serum or transfusion type may develop anywhere from thirty to a hundred and twenty days after transfusion, most cases occurring between the fiftieth and the ninetieth day.¹ The hepatitis following transfusions is pathologically indistinguishable from the hepatitis that is epidemic going under the term of epidemic infectious hepatitis. The evidence to date indicates that both types of hepatitis are due to viruses and that the virus of post-transfusion hepatitis is different from that causing epidemic hepatitis. In both types it is common to have a polymorphonuclear leukopenia in the peripheral blood and varying numbers of mononuclear cells not unlike those seen in infectious mononucleosis. This patient did show some of these "viral lymphocytes" in the peripheral blood. Either type of hepatitis may be mild, or may be severe and fulminating, with death ensuing within three or four days as in this case. At autopsy these cases show massive central necrosis of the liver lobules such

as that described by Dr Mallory,¹ and that is what I believe this case will show

CLINICAL DIAGNOSIS

Homologous serum jaundice

DR BALBONI'S DIAGNOSES

Hepatitis, transfusion type, with hepatorenal failure
Cholelithiasis
Partial colectomy
Multiple abscesses of liver?
Carcinomatosis of liver?

ANATOMICAL DIAGNOSES

Viral hepatitis, fulminant, homologous serum type
Arteriosclerosis, marked, aortic and coronary
Coronary thrombosis, old
Pulmonary embolism, left lower lobe
Cholelithiasis
Operative wounds resection of carcinoma of colon, colostomy, drainage of subdiaphragmatic abscess, ligation, bilateral, of superficial femoral veins

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Dr Balboni was correct in predicting that this patient would show evidence of hepatitis at autopsy. The liver looked grossly exactly like the ones we saw during the war and which Lucké and I² described as the fulminant form of hepatitis. The organ was only moderately shrunk and on section looked like an extremely severe nutmeg liver, with hemorrhagic and depressed lobular centers and pale, raised portal areas. Microscopically, the liver cells had almost completely disappeared, and the periportal tissues were densely infiltrated with mononuclear cells. It is not unusual for death to occur so rapidly that there is not time for much jaundice to develop. Profound coma is very characteristic and, when it develops before jaundice is apparent, may lead to suspicion

of various forms of intracranial disease. I remember a case in which a craniotomy was performed under the impression that the patient suffered from a subdural hematoma.

As Dr Balboni has already pointed out the pathological lesion of homologous serum jaundice is indistinguishable from that of epidemic hepatitis. There is no certain way to distinguish the two diseases except by the inoculation of human volunteers. The epidemic strain will infect when fed by mouth and can be demonstrated in the intestinal content. When the virus is given transcutaneously the incubation period is only two to three weeks as against the two to six months for the serum-jaundice strain. This patient developed jaundice some seventy days after his operation and transfusion therapy, so the incubation period was correct for serum jaundice and we may be reasonably confident of the diagnosis.

The remainder of the autopsy showed numerous lesions but none that seemed to bear upon his death. He had severe coronary sclerosis and one point of occlusion in the descending branch of the left coronary artery, but no evidence of infarction. A small pulmonary embolus was found in the left lower lobe. A stone was still present in the gall bladder but was causing no trouble. A few scars of old traumatic brain injury were present in the meninges, raising some suspicions that he might one time have been a prize fighter, but no acute lesion other than slight edema was found to account for his profound coma. This is usual in hepatitis. There was no evidence of metastasis or recurrence of the carcinoma, but the large bowel contained many polyps, at least one of which showed malignant cytology though no evidence of invasion. It seems probable therefore that further cancers of the bowel would have developed sooner or later.

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LAW AND THE LABORATORY

THE Commonwealth of Massachusetts, in 1877, established by state law the medical-examiner system to replace the gross inefficiency and corruption of the coroner system. For the first time in the history of the country a sovereign state recognized that a physician is better qualified than a layman to investigate sudden and violent deaths.

In seventy-two years of operation the Massachusetts medical-examiner system has slowly become the prototype for reform in other states and regional jurisdictions. In 1918 the five boroughs of New York City were placed under a chief medical examiner and his assistants, with responsibility for the investigation of medicolegal deaths in a population of seven million. In 1927 Essex County (Newark), New Jersey, followed suit. New Hampshire in 1903, Maine, in 1917, Rhode Island and

Maryland, in 1939, and Virginia, in 1947, replaced the lay coroner with the physician medical examiner. Maryland improved upon the system by the establishment of a central state laboratory with a chief medical examiner and regional medical examiners. Virginia followed with a similar plan, and this year Rhode Island has added a central laboratory and chief medical examiner.

Massachusetts has not been indifferent to the need for a central laboratory and expert technical staff for medicolegal investigation. For many years the pathologist medical examiners of Suffolk County served as consultants to the nonpathologist medical examiners of the other Massachusetts counties. Occasionally in the past, sometimes unhappily, a self-styled expert testified for the prosecution. One memorable murder trial brought forth the startling admission by such an expert that he had performed the wrong test for cyanide and had subsequently lost the victim's stomach and contents.

As the Massachusetts Department of Public Safety developed through the years expert facilities in ballistics, toxicology and trace laboratories were made available to the medical examiners, police and district attorneys of the State. Since 1940 a central consultation service for medicolegal autopsies has also been provided by the Department of Public Safety through the gratuitous services of the staff of the Department of Legal Medicine of Harvard Medical School. In ten years of activity, the highly trained medicolegal pathologists of that department have performed over 1400 autopsies at the request of medical examiners and district attorneys. Hundreds of thousands of miles have been traveled to every corner of the State without charge to the Commonwealth for professional services. In addition to this overwhelming contribution of time and skill to public service, the central medicolegal laboratory has given periodic formal instruction to state and city police officers of Massachusetts and other states concerning the preservation and interpretation of evidence related to violent deaths. Constant research has been carried on to clarify the mechanisms of sudden and violent death and thus to benefit the living.

An extraordinary degree of efficiency has resulted from this close interrelation of the pathologist,

toxicologist and ballistic and trace experts. The state-police investigators working with the district attorneys listen with confidence to the pathologist from the central laboratory, who has both experience and unlimited technical assistance at his call. The combination of state-police detective free from regional prejudice and expert forensic pathologist serving without fee does much to make Massachusetts safe for the innocent and perilous for the guilty.

THE FARNSWORTH SURGICAL BUILDING

MEDICAL activity on Bennet Street in the South End has been evolving for a century and a half. The evolution has been parallel to that of similar activities in other parts of the nation. The motivation has been the same: an interest in the care of the sick, in the training of those who profess to give that care, in the growth of the knowledge upon which the treatment of the sick is based and the prevention of sickness may be accomplished, and finally in the extension of the region served far beyond the Towne of Boston and out toward the borders of New England.

On May 26 another unit was opened with appropriate exercises and an opportunity for public inspection of the Farnsworth Surgical Building. At the corner of Bennet Street and Harrison Avenue, it will provide complete surgical equipment with 165 beds. The corridors are continuous with those of the Joseph H. Pratt Diagnostic Hospital and connect directly with the Ziskind Research Laboratories. Across Bennet Street is the Boston Dispensary, which connects directly with the Boston Floating Hospital. Diagonally across Harrison Avenue is the building now being remodeled for Tufts College Medical School.

This new building embodies many modern architectural features. Its five operating rooms, located in the basement and placed radially about the central servicing facilities, are entered only by those directly concerned with the work at hand, visitors being diverted to observation domes above. They may talk with the operating personnel, however, through a two-way intercommunication system. The observation domes are placed radially about the Stearns Auditorium (in honor of Dr. A. Warren

Stearns, Jr.), thus facilitating a combination of didactic and clinical teaching. They open from the main lobby of the building. In this way patients, students and operating personnel are provided with separate areas. In the well furnished rooms much may be found that is dear to the heart of hospital superintendents.

The dedicatory program included addresses by Dr. Edward D. Churchill, chief of the General Surgical Services of the Massachusetts General Hospital, and Chester I. Barnard, president of the Rockefeller Foundation and General Education Board. After the exercises tea was served, and there was a pleasant opportunity for leisurely inspection of the premises. The *Journal* salutes this new surgical unit of the New England Center Hospital.

MULTIPLE-SCLEROSIS SURVEY

ORGANIZATION and co-operative effort are providing expanded opportunities for both the study of disease and public education in health and sickness. One of the most recent of these collaborative case-finding ventures following hard upon those that have been conducted in the attack on tuberculosis, cancer, diabetes and heart disease is the current epidemiologic survey of multiple sclerosis.

Locally, the multiple-sclerosis survey in Boston and Brookline, in which the co-operation of all physicians is sought, is being conducted by the Department of Epidemiology of the Harvard School of Public Health. Aiding in the study are the Hospital Council of Boston, the Committee on Public Health of the Massachusetts Medical Society and the local district medical societies. Other regional studies being sponsored by the National Multiple Sclerosis Society and activated by grants-in-aid are either in progress or planned for the near future in New Orleans, San Francisco, Denver and Winnipeg. All will be conducted in co-operation with local schools of medicine or public health.

The purpose of the multiple-sclerosis survey, according to a release from the Harvard School of Public Health, is to determine the prevalence and distribution of the disease and to evaluate apparent differences in morbidity and mortality related to geography, climate, race and other factors. All

physicians in the areas designated are being requested, by individual letter, to provide information on appropriate forms on patients with multiple sclerosis seen within the past five years. The data will be used only for statistical purposes.

A young girl, near Philadelphia, laboring under some form of lunacy, by pretending to hold conversation with the Lord, is stirring up all the crazy people in the region, who flock in crowds to see one more possessed than themselves
Boston M & S J., July 25, 1849

MASSACHUSETTS MEDICAL SOCIETY



NORFOLK DISTRICT WOMAN'S AUXILIARY

The following officers for 1949-1950 were recently elected by the Woman's Auxiliary of the Norfolk District Medical Society: president, Mrs. John B. Hall, president-elect, Mrs. Joseph L. Tansey, vice-president, Mrs. David L. Lionberger, treasurer, Mrs. Benjamin Sachs, recording secretary, Mrs. Elliott Bresnick, and corresponding secretary, Mrs. David L. Halbersleben. The Advisory Council consists of Mrs. John W. Spellman, Mrs. Edward C. Smith, Mrs. W. Richard Ohler, Mrs. James D. Hepburn, Mrs. Norman A. Welch, Mrs. Leighton F. Johnson, Mrs. George W. Papen, Mrs. C. J. E. Kickham, Mrs. George F. Wilkins, and Mrs. Carlton E. Allard. The officers of the standing committees are as follows: Membership, Mrs. Harold N. McKinney, chairman, and Mrs. H. S. Levine, co-chairman; Public Relations and Publicity, Mrs. George F. Wilkins, chairman; Legislative, Mrs. Solomon L. Skvirsky, chairman; Ways and Means, Mrs. Goodwin A. Johnson, chairman, and Mrs. Newton C. Browder, co-chairman; Entertainment and Program, Mrs. John W. Spellman, chairman, and Mrs. Joseph L. Tansey, co-chairman; Hospitality, Mrs. Samuel Nadel, chairman, and Mrs. Arthur L. Gaetani, co-chairman; and Time and Place, Mrs. George W. Papen, chairman, and Mrs. Edward C. Smith, co-chairman. The historian is Mrs. Fedele M. Failace.

DEATHS

HULL — Ira B. Hull, M.D., of Gloucester, died on July 9. He was in his sixty-seventh year.
Dr. Hull received his degree from Harvard Medical School in 1912.
His widow survives.

PARKER — Ernest L. Parker, M.D., of Cohasset, died on January 18. He was in his seventy-first year.
Dr. Parker received his degree from Harvard Medical School in 1894.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

CARON — Damase Caron, M.D., of Manchester, died on June 9. He was in his seventy-fourth year.
Dr. Caron received his degree from University of Montreal Faculty of Medicine in 1900.
His widow, three daughters, three sons, eight grandchildren and two brothers survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

TETANUS TOXOID AVAILABLE FROM BIOLOGIC LABORATORIES

The Division of Biologic Laboratories of the Massachusetts Department of Public Health has received a license from the National Institutes of Health to produce and distribute tetanus toxoid, fluid.

The value of tetanus toxoid immunization was amply shown during World War II. In civil life it is especially useful to protect persons whose occupations expose them to the danger of cuts, burns or abrasions contaminated with dirt. The toxoid eliminates the necessity of repeated prophylactic doses of tetanus antitoxin, a horse-serum product, to such persons.

The toxoid is available in packages containing three 1-cc vials, for immunizing one person, and in large 20-cc vials for clinic use. The package containing three 1-cc vials may be obtained from biologic distribution stations or by direct request to the Biologic Laboratories, 375 South St., Jamaica Plain, 30, Massachusetts. The 20-cc vials will not be stored by the biologic distribution stations and should be obtained directly from the Division of Biologic Laboratories.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JUNE, 1949

DISEASE	RÉSUMÉ		
	JUNE 1949	JUNE 1948	SEVEN YEAR MEDIAN
Chancroid	4	0	1*
Chicken pox	1978	1665	1400
Diphtheria	40	35	15
Dog bite	1644	1537	1414
Dysentery bacillary	1	28	2
German measles	665	191	199
Gonorrhea	254	310	355
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	1	1*
Malaria	1	0	12
Measles	1352	6540	7652
Meningitis meningococcal	6	4	15
Meningitis Pfeiffer bacillus	8	7	4
Meningitis pneumococcal	5	0	4
Meningitis staphylococcal	0	0	0
Meningitis streptococcal	1	0	0
Meningitis undetermined	2	7	6
Mumps	1004	2031	966
Polio myelitis	29	3	2
Salmonellosis	5	8	8
Scarlet fever	385	912	898
Syphilis	231	203	373
Tuberculosis pulmonary	198	237	241
Tuberculosis other forms	14	15	21
Typhoid fever	2	5	3
Undulant fever	2	5	5
Whooping cough	466	102	05

*Five year median

COMMENT

Diseases above the seven-year median were chicken pox, diphtheria, dog bite, German measles, Pfeiffer-bacillus meningitis, pneumococcal meningitis and poliomyelitis.

Diseases below the seven-year median were measles, meningococcal meningitis and scarlet fever.

Chicken pox was at the highest level ever recorded in June.

Diphtheria still remains unusually prevalent for this season. German measles is still high for the season although the prevalence is less than half that of the previous month.

The incidence of poliomyelitis for the month of June was the highest since the disease has been reportable, however, the cases still remain scattered, with some concentration in Milton and Lynn.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Belmont, 1, Boston, 34, Brookline, 1, Cambridge, 1, Medfield, 1, New Bedford, 1, Salisbury, 1, total, 40.

Dysentery, bacillary, was reported from Waltham, 1, total, 1.

Infectious hepatitis was reported from Haverhill, 1, Waltham, 2, total, 3.

Malaria was reported from Newton, 1, total, 1.

Meningitis, meningococcal, was reported from Cambridge, 1, Hingham, 1, Holden, 1, Lynn, 1, Springfield, 1, Watertown, 1, total, 6.

Meningitis, Pfeiffer-bacillus, was reported from Lawrence, 1, Lowell, 2, Pittsfield, 1, Stoneham, 1, Stow, 1, Wellesley, 1, Worcester, 1, total, 8.

Meningitis, pneumococcal, was reported from Boston, 1, Cambridge, 1, Lynn, 2, Wakefield, 1, total, 5.

Meningitis, streptococcal, was reported from Brockton, 1, total, 1.

Meningitis, undetermined, was reported from Framingham, 1, Grafton, 1, total, 2.

Poliomyelitis was reported from Boston, 3, Brookline, 1, Cambridge, 1, Canton, 1, Dennis, 1, Everett, 1, Haverhill, 1, Hudson, 1, Lawrence, 1, Leominster, 1, Lynn, 6, Milton, 5, Newburyport, 2, Somerville, 1, Waltham, 1, Watertown, 1, Worcester, 1, total, 29.

Salmonellosis was reported from Boston, 2, Braintree, 1, Brookline, 1, Worcester, 1, total, 5.

Septic sore throat was reported from Boston, 4, Cambridge, 1, Medford, 1, Newburyport, 1, Quincy, 1, total, 8.

Tetanus was reported from Wakefield, 1, Whitman, 1, total, 2.

Trichinosis was reported from Boston, 1, Salem, 1, total, 2.

Typhoid fever was reported from Peabody, 1, Plymouth, 1, total, 2.

Undulant fever was reported from Danvers, 1, Lunenburg, 1, total, 2.

MISCELLANY

AMERICAN COLLEGE OF CHEST PHYSICIANS

Dr Dwight E. Harken, of Boston, presented a paper on "Experiences in Cardiac Valve Surgery" at the fifteenth annual meeting of the American College of Chest Physicians, held in Atlantic City, New Jersey, June 2-5.

Dr Richard H. Sweet, also of Boston, presented a paper entitled "Recent Advances in Esophageal Surgery."

The following physicians from the New England states received fellowship certificates at the Convocation held at the Ambassador Hotel, Atlantic City, on June 4: Dr Maxwell J. Antell, of Bridgeport, Connecticut; Dr Francis D. T. Bowen, of Newington, Connecticut; Dr Arthur H. Chernoff, of Saugus, Massachusetts; Dr Gisela K. Davidson, of Portland, Maine; Dr Francis E. O'Brien, of Haydenville, Massachusetts; and Dr Arthur D. Ward, of Worcester, Massachusetts.

BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Technik der kinderärztlichen Differentialdiagnostik für Studierende und praktische Ärzte. By Prof. Dr. Alphons Solch, chief of the Karolinen-Kinderspitale der Stadt Wien. 8° cloth, 384 pp., with 22 tables. Basel: Benno Schwabe & Co., 1948. Gebunden Fr. 20.

This textbook on the technic of the differential diagnosis of children's diseases is divided into three parts: general principles of diagnosis, differential diagnosis by symptoms, and regions and organs. The volume is well published and should prove valuable to German-reading physicians interested in pediatrics.

The Practice of Endocrinology. Edited by Raymond Greene, M.A., D.M., M.R.C.P. 8° cloth, 366 pp., with 53 illustrations and 91 figures. London: Eyre and Spottiswoode (Publishers), Limited, 1948. 52s. 6d. The Practitioner Textbooks.

This composite textbook is the joint work of seven specialists and covers the whole field of endocrinology. The text was completed in the spring of 1946, but its publication was delayed because of printing difficulties. An insert reviews some of the important literature of 1947. The material is well arranged. There is a comprehensive index, and the type, printing and paper are excellent. The volume, which weighs 2½ pounds and is easy to handle, is a concrete example of the possibility of using a soft light paper for large volumes. The work represents the British point of view but should be in all medical libraries and in all collections on the subject.

An Introduction to Gastro-Enterology. By Walter C. Alvarez, M.D., professor of medicine, University of Minnesota, Mayo Foundation, and senior consultant, Division of Medicine, Mayo Clinic. Fourth edition, revised and enlarged. 4° cloth, 903 pp., with 269 illustrations. New York: Paul B. Hoeber, Incorporated, 1948. \$12.50.

This fourth edition of a standard treatise has been thoroughly revised. Over 400 articles and books appearing since the third edition (1940) have been noted throughout the text. Much material has been added in the chapters on the pylorus, the nerves running to the bowel and to the gall bladder, the functions of the colon, flatulence, the electro-enterogram, technical methods and apparatus, and vagotomy in man. The text is concluded with a comprehensive bibliography of about 2800 titles. There is a good index. The type and printing are excellent. The volume weighs over 5 pounds and is not easy to handle. The relatively few illustrations do not justify the use of a heavy coated paper. The book should be in all medical libraries and in all collections on the subject.

Technic of Medication. By Austin Smith, M.D., C.M., M.Sc., director, Division of Therapy and Research, and secretary, Council on Pharmacy and Chemistry, American Medical Association. 12° cloth, 255 pp. Philadelphia: J. B. Lippincott Company, 1948. \$4.00.

This volume is the successor to the *General Technic of Medication*, written by Dr. Bernard Fantus, and first published in 1926 and last in 1938. The present work retains some of the old material rewritten, and much new material has been included. The work is intended primarily for the medical student and intern but should prove useful to the general practitioner. It includes chapters on the prescription and on oral, parenteral, rectal and genitourinary administrations, and dermal and mucous-membrane applications. The book is well published and forms part of the *Lippincott Essentials Series*.

Diabetic Manual for the Doctor and Patient By Elliott P Joslin, M.D., Sc.D., medical director, George F Baker Clinic, New England Deaconess Hospital, and consulting physician, Boston City Hospital Eighth edition 12", cloth, 260 pp., with 51 figures and 24 tables Philadelphia Lea and Febiger, 1948 \$2.50

This standard manual has been fully revised and brought up to date. Emphasis is placed on new discoveries, such as the modification of protamine zinc insulin, making possible in many cases one injection instead of two as formerly required, the significance of uric acid diabetes, and the new avenues of experimentation that opens up a possible prevention of diabetes among relatives. The statistics presented by Dr Joslin are remarkable. In cases seen up to 1914 only 1 patient in 55 had lived over twenty years with the disease, but in the period 1944 to 1948 the number had increased to 1 in 4—a truly remarkable achievement. In 2659 children treated since 1938, 2235 were alive at the time of writing. The book is recommended for all public libraries and should be available to all diabetic patients and their families. The price is moderate and within their means.

Factors Regulating Blood Pressure Transactions of the second conference, January 8-9, 1948, New York Edited by B W Zweifach and Ephraim Sborr, Department of Medicine, Cornell University Medical College 8", paper, 170 pp New York Josiah Macy, Jr Foundation, 1948 \$2.75

This conference was participated in by 23 authorities from the United States and Canada. Ten of them presented papers for discussion on varying aspects of the subject. The book should be in all medical libraries and in the collections of physiologists and physicians interested in blood pressure.

District Nursing A handbook for district nurses and for all concerned in the administration of a district nursing service By Eleanor J. Merry, S.R.N., S.C.M., C.S.P., H.V. Cert of R.S.I., social studies cert., Bedford College, education officer, Queen's Institute of District Nursing, and examiner for the Royal Sanitary Institute, and Iris D. Irven, S.R.N., S.C.M., H.V. Cert of R.S.I., superintendent, Worcester City Nursing Association 12", cloth, 266 pp., with 18 figures and 16 plates Baltimore Williams and Wilkins Company, 1948 \$4.00

This small volume covers the whole field of district nursing (visiting nursing) as practiced in England. The text was printed in Great Britain. The publishing is excellent. The book forms part of *Baillière's Handbooks for Nurses*. It should be in all nursing collections.

Hematology By Cyrus C. Sturgis, M.D., professor of internal medicine and chairman of the Department of Internal Medicine, University of Michigan Medical School, and director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan 4", cloth, 915 pp., with 72 illustrations Springfield, Illinois Charles C. Thomas, 1948 \$12.50

This new work on hematology is based on the author's long experience supplemented by a knowledge of the literature of the subject. The material is well arranged. The author discusses in order the anemias, hemorrhagic states, the leukemias, malignant lymphoma and other special diseases of the blood. The two last chapters are on sternal puncture and blood transfusions and blood substitutes. An extensive bibliography of fifty-three pages concludes the text. There is a good index. The printing is done on a coated, filled, glaring paper, not necessary because the color plates are tipped into the volume. The volume weighs over 4 pounds, and much of the weight could have been saved by the use of another kind of paper. It is time that publishers began to think of the convenience of the reader and made their books as light as possible. The volume is recommended for all medical libraries and for all physicians interested in diseases of the blood.

Health Instruction Yearbook 1948 Compiled by Oliver E. Bird, Ed.D., M.D., F.A.P.H.A., professor of health education and director, Department of Hygiene School of Educa-

tion, Stanford University. With a foreword by Ray L. Wilbur, M.D., chancellor, Stanford University 8", cloth, 320 pp. Stanford, California Stanford University Press, 1948 \$3.50

This volume of a series inaugurated in 1943 is based upon 1514 articles read by the author, of which 321 were selected for condensation and publication. They were found in 100 different publications. It is interesting to note that nineteen selections were made from the *Congressional Record*. A bibliography of the articles follows the text. There are author and subject indexes. The book is well published and should be in all medical libraries and in all public-health collections. It affords an easy way of keeping up with the current literature on the subject.

"Hi-Ya Neighbor" By Ruth Stevens 8", cloth, 122 pp., with 34 illustrations New York Tupper and Love, Incorporated, 1947 \$2.00

Miss Stevens relates an interesting account of the "off-the-record" hours of the late President Roosevelt, spent at Warm Springs, Georgia, where he went for treatment of poliomyelitis. A number of interesting pictures of the buildings and of the President and other patients are interspersed throughout the text. There is a detailed account of his last day at Warm Springs, where he died on April 12, 1945.

Blood Clotting and Allied Problems Transactions of the first conference February 16-17, 1948, New York, New York Edited by Joseph E. Flynn, Department of Pathology, College of Physicians and Surgeons, Columbia University 8", cloth, 179 pp New York Josiah Macy, Jr Foundation, 1948 \$3.25

Sixteen authorities took part in this conference on blood clotting. There are a number of articles on protobromin and clotting time. The type and printing are excellent. The ring type of binding does not stand for durability. The volume should be in all medical libraries.

The Child in Health and Disease A textbook for students and practitioners of medicine By Clifford G. Grulee, M.D., Rusb professor of pediatrics, University of Illinois, the School of Medicine, attending pediatrician, Presbyterian Hospital, Chicago, chief editor, *American Journal of Diseases of Children*, and secretary of the American Academy of Pediatrics, and R. Cannon Eley, M.D., associate in pediatrics and communicable diseases, Harvard Medical School, chief of isolation service and visiting physician, Infants and Children's hospitals, Boston, and member of the Committee on Awards of the American Academy of Pediatrics 4", cloth, 1066 pp., illustrated Baltimore Williams and Wilkins Company, 1948 \$12.00

This comprehensive treatise on pediatrics is the joint work of 75 competent specialists. The whole field of the care and management of the child in health and disease is covered in extenso. To compress the large amount of text into one volume it was necessary to use a two-column format and a medium-sized type. Also, the use of filled paper makes the volume too heavy to handle easily—it weighs 5 pounds. A comprehensive index of sixty pages concludes the text. This new treatise should be in all medical libraries as a reference source.

Textbook of the Rheumatic Diseases Edited by W. S. C. Copeman, O.B.E., M.D., F.R.C.P., physician to the Rheumatism Department and lecturer in the Medical School, West London Hospital, physician to Arthur Stanley Institute of Rheumatic Diseases (Middlesex Hospital), Hunterian professor, R.C.S., senior physician, the Hospital of St. John and St. Elizabeth, and consultant for rheumatic diseases, Royal Hospital for Incurables, and consultant to L.C.C. 8", cloth, 612 pp., with 351 illustrations Baltimore Williams and Wilkins Company, 1948

This composite treatise is the work of 24 British authorities on rheumatic diseases. The whole field of the subject is covered, beginning with nomenclature and history and followed by the anatomy and physiology of pain and of the joints, discussions of the various rheumatic diseases,

diagnosis, pathology, radiology, chapters on the various methods of treatment, the psychiatric, social and industrial aspects and statistics. Indexes of authors and subjects conclude the book. The publishing is excellent in every way. The illustrations are particularly good, both of radiographs and plates in color. The printing was done in Great Britain. The book is recommended for all medical libraries and to all specialists on rheumatism.

Experimental Immunochemistry. By Elvin A. Kabat, Ph.D., associate professor of bacteriology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, New York City, and Manfred M. Mayer, Ph.D., associate professor of bacteriology, School of Hygiene and Public Health, Johns Hopkins University. With a foreword by Michael Heidelberger, Ph.D., professor of biochemistry, College of Physicians and Surgeons, Columbia University, and chemist to the Presbyterian Hospital, New York City. 8°, cloth, 567 pp., with 88 illustrations. Springfield, Illinois: Charles C. Thomas, 1948. \$8.75.

This book brings together the techniques employed in research in the field of immunochemistry. The emphasis has been placed on quantitative methods. For students and chemists not familiar with the subject, introductory material is provided in the early parts of the text, which is divided into four parts: immunologic and immunochemical methodology, applications and uses of quantitative immunochemical methods, chemical and physical methods and special procedures, and preparations. The printing is well done, with a good, large type on a light, nonglare paper. There is a good index. The book is an essential tool for the laboratory and should be in the reference collections of all medical libraries, and should be available to chemists and others interested in the subject.

The Renal Origin of Hypertension. By Harry Goldblatt, M.D., C.M., director, Institute for Medical Research, Cedars of Lebanon Hospital, and professor of pathology, School of Medicine, University of Southern California, Los Angeles. 8°, cloth, 127 pp. Springfield, Illinois: Charles C. Thomas, 1948. \$2.75.

In this short monograph, the author summarizes twenty years of experimental research and discusses the following problems: the production of experimental hypertension, pathologic changes in hypertensive animals, pathogenesis, the humoral mechanism, renin, hypertensinogen, hypertensin and other vasoconstrictor substances, and treatment. The importance of the subject is evidenced by its death rate. Arteriosclerotic diseases of the brain, heart and kidneys, associated with hypertension, cause about four times more deaths than cancer. The final chapter comprises a summary of the similarities and differences between human essential and experimental human hypertension. There is a good index. The volume is well published in every way. It forms part of the *American Lecture Series* and should be in all medical libraries.

The Parathyroid Glands and Metabolic Bone Disease. Selected studies. By Fuller Albright, M.D., associate professor of medicine, Harvard Medical School, physician, Massachusetts General Hospital, and consulting physician, Massachusetts Eye and Ear Infirmary, and Edward C. Reifenstein, Jr., M.D., consultant-in-charge, Department of Clinical Investigation, Sloan-Kettering Institute of Cancer Research, Memorial Hospital Cancer Center, New York City, and clinical research consultant, Ayerst, McKenna and Harrison, Limited, New York City. 8°, cloth, 393 pp., with 157 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$8.00.

The studies presented in this volume comprise in a way a summary of the work carried out on the metabolic ward of the Massachusetts General Hospital during the past twenty-four years. The articles include the normal and pathologic physiology of the parathyroid glands, clinical hypoparathyroidism and hyperparathyroidism, mode of action of vitamin D and dihydrotachysterol (A.T.10), general considerations of metabolic bone disease, osteoporosis, osteomalacia, poly-

ostotic fibrous dysplasia (*osteitis fibrosa disseminata*) and Paget's disease (*osteitis deformans*). There is a long bibliography, and author-and-subject indexes. The volume is well published and should be in all medical libraries.

The Clinical Apprentice. A guide for students of medicine. By John M. Naish, M.D. (Cantab.), M.R.C.P., and John Apley, M.D. (Lond.), M.R.C.P. With a foreword by Professor J. A. Ryle. 12°, cloth, 200 pp., with 71 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$4.50.

In this manual for interns the text is divided into two parts. The first, entitled "Examination at Leisure," discusses conditions in which there is ample time to make a complete diagnosis. The material in this part is arranged by the systems of the body, preceded by chapters of a general character. The second part, called "Examination of Acute Cases," is arranged by symptoms and considers means of establishing a provisional diagnosis on which to base immediate treatment in acute cases without undue disturbance of the patient. The symptoms singled out for discussion include the unconscious patient, the meningitic syndrome, high temperatures, acute breathlessness and convulsions. The material is well arranged, and there is a good index. The small volume is well published. The text was printed in Great Britain and naturally reflects the British point of view. The price seems excessive for such a small volume.

NOTICES

OPENINGS FOR PHYSICIANS

The Bureau of Reclamation of the Department of the Interior announces openings for two physicians at Coulee Dam, Washington, a town of 7500. Government-owned premises are for lease, in addition to which the lessee shall pay the United States for garbage disposal and refuse service, water and sewer service and electricity.

Sealed bids will be received until September 15 at 2:00 p.m. Further information may be obtained from the acting district manager of the Bureau of Reclamation at Coulee Dam.

EXAMINATIONS FOR APPOINTMENT IN NAVY MEDICAL CORPS

Examinations for the selection of candidates for appointment to the grade of lieutenant (junior grade) in the Medical Corps of the United States Navy will be conducted at all Navy Hospitals during the period September 12 to 16, 1949, inclusive.

Graduates of approved medical schools in the United States or Canada who have completed intern training in accredited hospitals or who will complete such training within four months of the date of the examination and who are physically and in other respects qualified, may be examined for appointment as lieutenant (junior grade) in the Medical Corps of the Navy. Candidates must be less than thirty-two years of age at the time of appointment.

Candidates will be required to appear before boards of medical examiners and supervisory examining boards at the Navy Hospital nearest their place of residence to demonstrate their physical and professional qualifications for appointment. After approval by the President of the United States and confirmation by the Senate, selected candidates will be issued appointment and orders assigning them to duty in a Navy medical facility for active service.

A lieutenant (junior grade) in the Navy Medical Corps receives pay and allowances totaling \$5011 a year if married and \$4575 50 if unmarried.

Detailed information concerning the form and procedure of application may be obtained from the offices of Naval Officer Procurement or from the Bureau of Medicine and Surgery, Navy Department, Washington 25, D.C. (Attn: Code-3424).

(Notices concluded on page xv)

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AUREOMYCIN THERAPY IN THE PULMONARY INVOLVEMENT OF PANCREATIC FIBROSIS (MUCOVISCIDOSIS)*

HARRY SHWACHMAN, M.D.† ALLEN C. CROCKER, M.D.,‡ GEORGE E. FOLEY,§ AND
PAUL R. PATTERSON, M.D.¶

BOSTON

THIS report is concerned with aureomycin, in the treatment of patients with pancreatic fibrosis (cystic fibrosis of the pancreas).^{1,2} Numerous advances in the understanding of the nature of the disease, development of diagnostic procedures and clinical management have been made in a series of correlated studies carried out at the Boston Children's Hospital.³⁻⁵ The common notion that this is a rare disease and that the immediate prognosis is always poor is no longer tenable. Another misconception perhaps based on historical and nosologic grounds, is the view that this is a disease solely of the pancreas and that involvement of other organs, chiefly the lungs and liver, is secondary to the disorder in the pancreas. Farber⁹ described the generalized nature of this disease and has introduced the term "mucoviscidosis" to signify the essential alteration in mucus-secreting glands as a primary defect. There is sufficient clinical variation in the disease to indicate that different degrees of involvement in different organs exist. However, one is struck by the frequency of pulmonary symptoms early in the disease in the majority of patients. These symptoms are cough, often paroxysmal and at times suggestive of pertussis or wheezing respirations with the production of thick, tenacious mucus. Atelectasis and emphysema with infection, primary or secondary, are the chief features as seen clinically and as demonstrated by roentgenograms. Indeed, the roentgenogram of

the chest may be sufficiently characteristic to suggest the diagnosis of pancreatic insufficiency.¹⁶ The respiratory rate may be increased, and the chest often becomes rounded with increased anteroposterior diameter. Vital capacity and exercise tolerance are diminished. Clubbing of the fingers and cyanosis may follow. If the pulmonary lesion advances, irreversible changes such as bronchiectasis and multiple staphylococcal abscesses may develop. A constant feature is the laboratory finding of *Staphylococcus aureus* in the nasopharynx of these patients.

The management of a patient with this disease involves consideration of replacement therapy in the form of pancreatin, the use of protein hydrolysates, the administration of a high-calorie diet with some restriction of fat, and liberal supply of vitamins including water-miscible vitamin A. The pulmonary infection is perhaps superimposed upon a more fundamental defect as yet not fully understood and its successful therapy is a problem of grave concern. The introduction of the sulfonamides, penicillin and streptomycin marked a signal advance in the management of the pulmonary infection. The use of aerosol therapy with penicillin or streptomycin, alternating with variable periods of oral sulfadiazine has become part of routine management. This combined form of therapy under constant medical supervision has proved beneficial to most patients. The cost of the therapy outlined above is high. The administration of aerosol therapy to small infants is difficult and even the older child is not always fully co-operative. The substitution of an orally effective antibiotic such as aureomycin for the expensive and more difficult form of aerosol therapy has obvious merits.

Aureomycin has been shown to have a wide range of activity against bacteria, rickettsia and certain viruses.^{2,27} It has been found to be effective in vitro against the staphylococcus species isolated from patients with pancreatic fibrosis as determined

*Presented in part at the annual meeting of the Society for Pediatric Research, Atlantic City, May, 1949.

From the Division of Laboratories and Research and the Department of Medicine, The Children's Medical Center, and the Departments of Pediatrics and of Pathology, Harvard Medical School.

This study was supported in part by a grant from the Grant Foundation, Incorporated.

†Associate in pediatrics, Harvard Medical School; associate physician and chief, Division of Clinical Pathology, The Children's Medical Center.

House officer, Division of Clinical Pathology, The Children's Medical Center.

‡Research associate in pathology and bacteriology, The Children's Medical Center.

§Research fellow in pediatrics, Harvard Medical School; fellow in pediatrics and pathology, The Children's Medical Center.

¶A generous supply of aureomycin for use in this study was furnished by the Lederle Laboratories, New York City.

in this laboratory. A modest amount of experience in the treatment of a variety of infections in children, including some caused by the staphylococcus species, indicated that a satisfactory response could be expected and that toxic effects would be minimal. The favorable clinical response to aureomycin of a three-year-old patient with pancreatic fibrosis and extensive pulmonary involvement indicated that further use of the drug was warranted.

PLAN OF STUDY

Early in the course of this study aureomycin was used only to replace aerosol therapy with peni-

as a basis for comparison, particularly when the only change in the plan of therapy was the substitution of aureomycin for other antibiotic agent. The same dietary schedule, including the use of pancreatin, was followed. In all the cases considered in this study the diagnosis was confirmed by duodenal-fluid assay for trypsin,* and in many cases corroborated by abnormal glycine absorption after an oral gelatin feeding²⁰ and by the failure to find trypsin in the stools.²¹ A total of 35 patients have been treated and followed for at least a two-month period after the institution of aureomycin therapy. The longest period of observation extends over

TABLE 1 *In Vitro* Aureomycin Sensitivity of Micro-organisms Isolated from Thirty-Two Miscellaneous Infections

MICRO ORGANISM	NO OF STRAINS TESTED	AUREOMYCIN SENSITIVITY					
		STRAINS REQUIRING MORE THAN 40 MICROGM /cc.	STRAINS REQUIRING MORE THAN 2.5 MICROGM /cc.	STRAINS REQUIRING MORE THAN 1.0 MICROGM /cc.	STRAINS REQUIRING MORE THAN 0.5 MICROGM /cc.	STRAINS REQUIRING MORE THAN 0.25 MICROGM /cc.	STRAINS REQUIRING MORE THAN 0.064 MICROGM /cc.
<i>E. coli</i>	7	7	—	—	—	—	—
<i>A. aerogenes</i>	3	1	1*	—	—	—	—
<i>P. aeruginosa</i>	9	9	—	—	1*	—	—
<i>H. influenzae</i>	2	—	—	1	—	—	—
<i>Staph. aureus</i>	4	—	—	—	—	—	1
<i>Pr. vulgaris</i>	2	2	—	—	—	3	1
<i>Neisseria catarrhalis</i>	3	1	—	—	—	—	—
<i>Beta streptococcus</i>	1	1	—	—	1	1	—
<i>Corynebacterium diphtheriae</i>	1	1	—	—	—	—	—

*Type B

cillin or streptomycin, or both. However, as experience was gained the drug was administered more liberally, even to patients with minimal pulmonary signs, who at the time were not receiving antibiotic therapy. These patients were followed in the Nu-

four and a half months. At least 15 additional patients could be included if the data were analyzed on a shorter observation period. In the latter group the response has been similar to that observed in patients followed over a longer time. Frequent laboratory observations were made, including roentgenograms of the chest, white-cell counts and nose and throat cultures, the last being taken on each visit. The patients considered ranged in age from five weeks to twelve years.

TABLE 2 *In Vitro* Sensitivity of *Staph. aureus* Isolated from Nasopharynx of 42 Patients with Pancreatic Fibrosis before Treatment with Aureomycin

CONCENTRATION OF DRUG* REQUIRED	STRAINS SENSITIVE TO AUREOMYCIN	STRAINS SENSITIVE TO STREPTOMYCIN	STRAINS SENSITIVE TO PENICILLIN
More than 40	5 (12%)	11 (44%)	19 (74%)
20	3	—	—
10	4	1	—
0.5	10	—	—
0.25	8	—	—
0.125	10	—	—
0.064	1	6	2
0.032	1	4	3
0.008	—	1	—
0.004	—	2	2
Totals	42	25	26

*For aureomycin, microgm per cubic centimeter; for streptomycin, mg per cubic centimeter; and for penicillin, Oxford units per cubic centimeter.

DOSAGE

Aureomycin is supplied in gelatin capsules, a form inconvenient to dispense to infants and young children. Inasmuch as the drug is unstable in solution,^{28, 29} the capsule was opened, and the dried powder given with food or drink. The drug may be rejected because of its bitter taste.† However, most parents have succeeded in its administration. At first the drug was given four times a day, but more recently it has been given in divided or even in single daily doses. An effort has been made to provide the minimal effective amount for each patient. This is roughly 20 to 30 mg per kilogram of body weight, or 125 to 250 mg daily, in divided

*In 2 patients (Cases 9 and 35) duodenal intubation was not performed. However, the diagnosis was made on clinical grounds in addition to abnormal gelatin absorption and absent stool trypsin.

†Aureomycin flavored powder (speroids) has been employed in a small number of cases with favorable results. This preparation, which can be added to milk or other fluids, overcomes the unpleasant taste.

tritional Clinic on an outpatient status or as private patients and were seen by the same observers at intervals of two to five weeks. Many of the older patients have been followed for several years in the same clinic and their response to antibiotic therapy is well known. This background served

or single doses for infants and 250 to 750 mg per day in two or three divided doses for children

BACTERIOLOGIC STUDIES

The flora of the upper respiratory tract was determined on each patient by separate nasopharyngeal and throat swabs taken before therapy and at each subsequent visit. The staphylococcus species isolated were studied for sensitivity to various antibiotics.

In vitro sensitivity to aureomycin was determined by a tube-titration method similar to that employed for penicillin sensitivity.³⁰ Aureomycin is diluted

These determinations are considered to be of only relative value, inasmuch as an arbitrary concentration of 40 microgm per cubic centimeter has been selected as an end point in this study. It should be emphasized that in no case has in vitro sensitivity influenced either the use or the dosage of the drug. Aureomycin blood and urine levels have not been undertaken in view of the difficulties inherent in such determinations.³²

Table 1 summarizes the in vitro sensitivities of the micro-organisms isolated from 32 patients other than those with pancreatic fibrosis. *Haemophilus influenzae* and *Staph aureus* were the most sensitive

TABLE 3 Response to Aureomycin Therapy

CASE NO	SEX	AGE AT APPEARANCE OF FIRST PULMONARY SYMPTOMS	AGE AT TIME OF DIAGNOSIS	PRESENT AGE	GENERAL CONDITION AT START OF THERAPY	WEIGHT AT START OF THERAPY	DURATION OF THERAPY	CLINICAL RESPONSE
		mo	mo	mo		lb	oz	wk
1	M	1½	1	2	Poor	6	3	4
2	F	1	4	6	Poor			7
3	F	2½	2	9	Patient acutely ill	8	6	10
4	M	1½	1	11	Fair	12	8	14
5	F	1½	9	11	Poor	11	7	8
6	M	1½	2½	13	Fair	16	3	12
7	M	1½	6	14	Poor	13	13	10
8	F	1	(3 days)	14	Good	19	0	7
9	M	5	5	17	Good	19	6	1
10	M	1½	1½	17	Poor	21	2	16
11	M	9	7	17	Poor	11	6	9
12	F	1	2	19	Poor	20	9	16
13	F	1	1	20	Very poor	16	6	9
14	F	1½	1½	20	Very poor	23	0	12
15	F	3½	16	20	Poor	20	2	8
16	M	3	18	21	Fair	25	0	8
17	F	3½	16	22	Poor	16	2	11
18	M	6	6	24	Patient severely ill	23	0	12
19	M	18	25	26	Very poor	23	0	4
20	F	2½	2	27	Poor	20	0	12
21	F	20	25	28	Fair	22	15	8
22	M	3½	11	28	Poor	18	4	17
23	F	3	11	31	Poor	24	4	15
24	M	24	24	36	Good	26	0	9
25	F	1½	8	44	Very poor	19	0	18
26	M	2½	28	47	Fair	32	0	8
27	M	4	5	53	Poor	33	8	12
28	M	1½	54	57	Fair	33	0	10
29	F	4	15	65	Fair	35	4	8
30	M	4	52	73	Poor	39	0	8
31	M	34	40	79	Poor	27	0	9
32	F	36	19	111	Fair	45	0	8
33	M	90	66	115	Poor	41	0	11
34	F	72	94	117	Fair	49	4	16
35	F	72	139	144	Grave	61	0	1½

*Private patients of Dr. R. M. Smith
†Rubeola developed 18 days after aureomycin was started
‡Rubella developed 1½ mo after aureomycin was started

so that four times the desired concentration is contained in a volume of 0.5 cc of tryptic digest broth and diluted serially by 50 per cent decrements. An eighteen-hour broth culture of the micro-organism to be tested is diluted 1:100, and 1.5 cc of this dilution is added to each 0.5-cc dose of aureomycin. The range of final concentrations usually employed is 4.0 to 0.004 microgm per cubic centimeter. The tubes are incubated at 37°C for sixteen hours. The last tube showing complete inhibition of growth is taken as the end point. Since aureomycin rapidly loses potency in solution the end points at sixteen hours may be higher than those at twelve hours. The composition of the medium also influences the rate of loss of aureomycin activity.³¹ However, with standardized conditions the method outlined above checks within one tube in duplicate titrations

of the species included in this small series. It is interesting to note that all strains of *Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus vulgaris* required more than 40 microgm per cubic centimeter for inhibition, since it has been reported that aureomycin is relatively ineffective against *Ps aeruginosa* and *Pr vulgaris*.^{29, 33} The greater resistance of these species is further reflected in their appearance or persistence in the nasopharynx of patients receiving aureomycin.

RESULTS

In Vitro Studies

Table 2 presents a comparison of the in vitro aureomycin, penicillin³⁰ and streptomycin³¹ sensitivities of the strains of *Staph aureus* isolated

from the nose and throat cultures of cases of pancreatic fibrosis. Most of these patients had previously received penicillin or streptomycin, or both, but not aureomycin at the time these determinations were done. As may be seen in Table 2 only 12 per cent of the strains tested required a concentration of more than 40 microgm per cubic centimeter of aureomycin for inhibition, as compared to 44 and 74 per cent requiring more than 40 mg of streptomycin or 40 Oxford units of penicillin respectively. The number of strains resistant to penicillin and streptomycin in this series may be

on aureomycin titrations done on a single fishing from each culture. However, in other cases, multiple fishings from the same culture yielded identical sensitivities when examined in the same manner. It seems unlikely that the increased resistance observed in these 7 patients was due to variations in the sensitivity of different fishings of the same strain, as has been true of streptomycin.³⁵

Pulmonary Signs and Symptoms

The most striking effect of aureomycin therapy was the consistent amelioration of cough, dyspnea

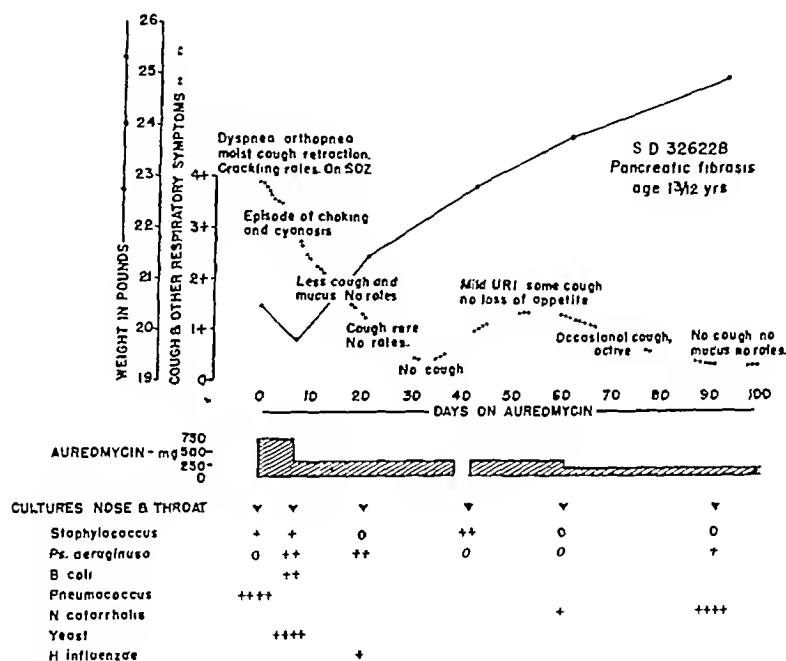


FIGURE 1 Summary of the Effect of Aureomycin Therapy on the Course in Case 12
Note abatement of respiratory symptoms and marked weight gain

in part a reflection of previous exposure to these antibiotics. However, it has been observed in a large series of strains studied in this laboratory that *Staph aureus* is frequently penicillin resistant and streptomycin sensitive, both before and after exposure to the antibiotics.³⁵

The flora of the nose and throat was essentially unchanged in many patients after they had received aureomycin. Clinical improvement bore no relation to bacteriologic improvement, the former being commonly and the latter only rarely observed. When a staphylococcus species was isolated during the course of therapy, repeated in vitro sensitivity to aureomycin was determined. Such data were obtained on 18 patients. In 7 cases an increase in resistance ranging from fourfold to thirty-two-fold was observed. On the other hand there were only 2 cases in which repeat titrations failed to check within one tube. These observations were based

and respiratory distress. Fever, if present, was likewise favorably affected. Response was rapid, a change usually occurring within two or three days. Cough, which often kept the child awake through the night or occasionally induced vomiting, either stopped abruptly or became minimal. In some cases the parents stated that for the first time in weeks the child slept through the night without cough. This excellent response was observed in 31 of the 35 patients (Table 3). Two patients (Cases 26 and 32) showed only minimal improvement, probably because of inadequate dosage. One child (Case 35), the oldest in the series, had extensive bilateral bronchiectasis of six years' duration and a ten-day course of drug had no noticeable effect. As would be expected the physical examination of the chest showed little or no alteration in the fixed hyperexpanded thorax. Auscultatory signs varied, in some cases there was complete disap-

pearance of rales and rhonchi, and in others these signs persisted. In a few patients with bronchiectasis, clinical improvement appeared without any significant change in the physical findings in the chest.

General Condition

Improvement in disposition and well-being often accompanied the relief of respiratory symptoms. Two of the older boys felt so well that for the first time they were able to compete in the vigorous activities enjoyed by their playmates. In addition, a striking improvement in appetite was noted in many patients. This is of interest in view of the voracious appetites many of these patients possessed before pulmonary infection supervened. Weight gain was noted frequently and was striking in some patients (Fig 1).

Effect on the Stools

The action of aureomycin on the gastrointestinal tract deserves special attention. Nausea and vomiting are mentioned as frequent side effects in the adult. These symptoms were rarely encountered in this series of patients. The stools increased in number and became loose in the majority and watery in a few cases. The offensive odor commonly associated with the stools of these patients became less noticeable. The stools took on a yellowish or greenish color. There appears to be a rough relation between dosage and bowel activity. In the infant age group 500 mg or more a day may produce a troublesome diarrhea. This is likely to stop after twenty-four to forty-eight hours off the drug. In 1 patient (Case 9) the drug had to be discontinued after three separate trials, because of severe diarrhea even on minimal dosage. It should be noted that some of the most encouraging gains in weight were observed in patients who had diarrhea. In patients other than those with pancreatic fibrosis who were treated with aureomycin in the same dosage schedule diarrhea did not develop.

The effect of aureomycin on the aerobic bacterial flora of the stool has been studied in a small series of cases. The results varied from no effect in most cases to complete disappearance of the normal flora while the patient was receiving therapy. In several cases the persistence or appearance of *Ps aeruginosa* or *Pr vulgaris* was observed in the stool after the disappearance of the usual aerobic flora.

Stool Trypsin

The absence of tryptic activity in the stool is unaltered by this drug in patients receiving inadequate or no pancreatic therapy. On adequate pancreatic therapy stool trypsin is regularly demonstrated regardless of whether or not the patient is receiving aureomycin.

White-Cell Count

The white-cell count does not necessarily reflect the activity of the pulmonary infection. Except during acute episodes this measurement is not very

useful. In some cases the elevated count returned to normal levels after aureomycin therapy, but this was not a constant observation.

Roentgenograms

In most cases roentgenograms were taken previous to aureomycin therapy and at frequent intervals.

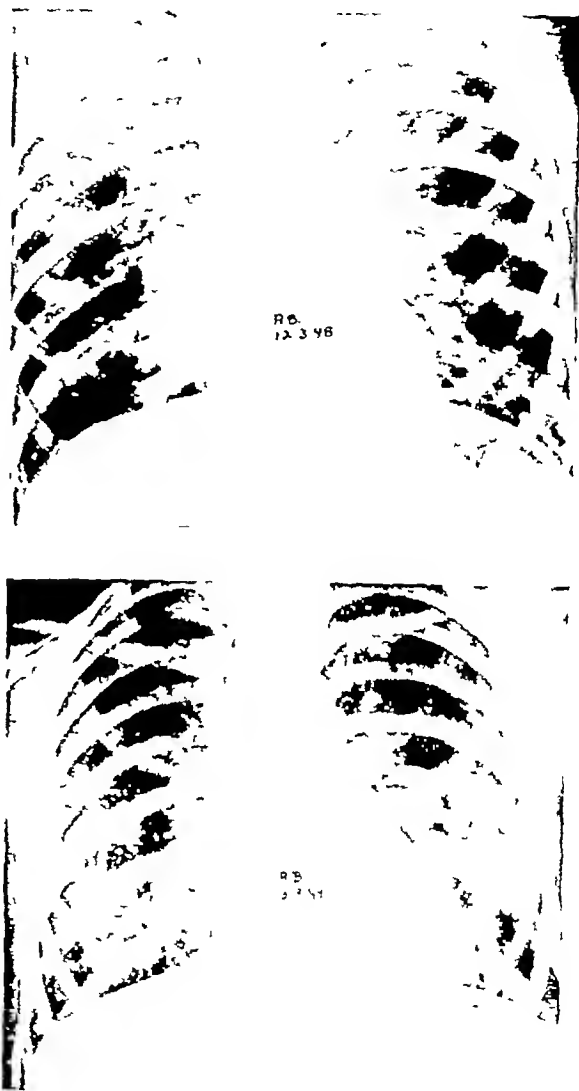


FIGURE 2 Roentgenograms of the Chest in Case 28 Taken before Aureomycin Was Started (Upper Film) and Three Months Later (Lower Film) Showing Improvement in the Extent of the Pulmonary Involvement

thereafter. Some improvement was seen, but this was not comparable to the excellent clinical response (Fig 2).

The Problem of Relapse

Aureomycin was discontinued in several patients after varying periods. Within three to seven days a relapse occurred, particularly in those with ex-

tensive pulmonary involvement. Readministration of the drug resulted in improvement. No refractoriness to the drug developed in this short period of observation.

Data from 2 patients are presented in Figures 2 and 3 to illustrate the nature of the response to aureomycin and to emphasize many of the statements made above. These figures are self-explanatory. In addition a summary of the treated cases arranged according to age of patient is presented in Table 3.

Figure 4 demonstrates the appearance of a patient (Case 19) taken before and after four weeks of aureomycin therapy with a dose of 125 mg twice

tration of aureomycin to small infants with pancreatic fibrosis to delay or prevent the appearance of pulmonary infection appears to be rational. It may likewise prove worth while to follow carefully the siblings of patients with known pancreatic fibrosis and babies with meconium ileus so that prophylactic aureomycin therapy can be instituted when indicated. That the drug can be given continuously over a long period without untoward effect has been demonstrated.

Although aureomycin is presumably effective because of its antibacterial properties, the persistence of the same bacterial flora in the nasopharynx despite the marked clinical improvement observed

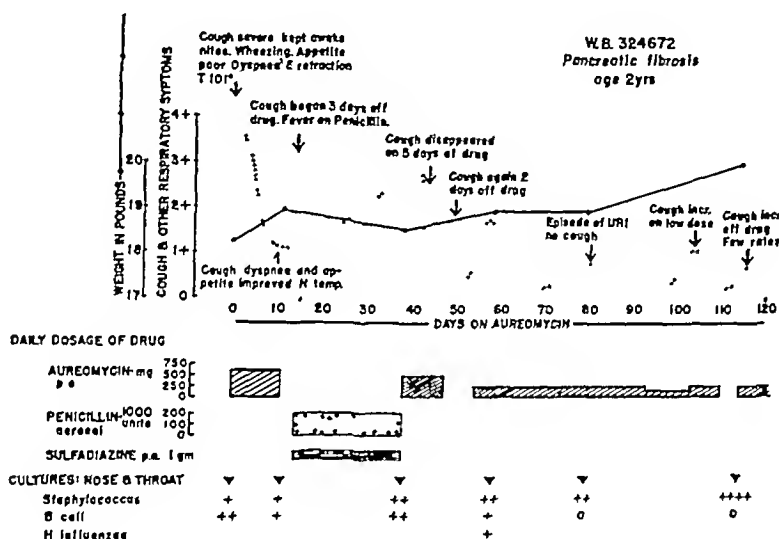


FIGURE 3 Summary of the Course in Case 22 during the Period of This Study. Note that although penicillin aerosol and sulfadiazine did not control the respiratory symptoms, aureomycin repeatedly resulted in improvement in cough. It should also be noted that cessation of the drug or inadequate dosage caused a recurrence of symptoms.

a day. As in the remaining cases no other antibiotic was used concomitantly.

DISCUSSION

The introduction of a new, effective antibiotic in the management of patients with the pulmonary complications of pancreatic fibrosis simplifies the present mode of therapy. Inasmuch as the drug is effective in small oral doses and possesses few undesirable properties, it may become a most useful adjunct to the other therapeutic agents used in the treatment of this condition. The prompt return of symptoms when the drug is discontinued should be emphasized. That such an agent will be most effective when administered early in the course of the pulmonary disease is obvious. It is equally clear that the drug will be of little ultimate value in advanced bronchiectasis. Prophylactic adminis-

tration of aureomycin to small infants with pancreatic fibrosis to delay or prevent the appearance of pulmonary infection appears to be rational. It may likewise prove worth while to follow carefully the siblings of patients with known pancreatic fibrosis and babies with meconium ileus so that prophylactic aureomycin therapy can be instituted when indicated. That the drug can be given continuously over a long period without untoward effect has been demonstrated.

Although aureomycin is presumably effective because of its antibacterial properties, the persistence of the same bacterial flora in the nasopharynx despite the marked clinical improvement observed

in vivo exposure. However, these patients continued to show clinical improvement on the same dosage schedule despite increasing in vitro resistance.

The appearance of *Pr vulgaris*, *Ps aeruginosa* and fungi in the nasopharynx of patients treated with aureomycin, overgrowing or replacing the initial bacterial flora, is reminiscent of similar

of cough, improved general well-being, increased appetite and weight gain. An increase in the number and looseness of stools was noted in most patients. The drug had to be discontinued in 1 patient because of severe diarrhea. No other untoward effects were encountered. The discontinuance of the drug resulted in the prompt reappearance of symptoms

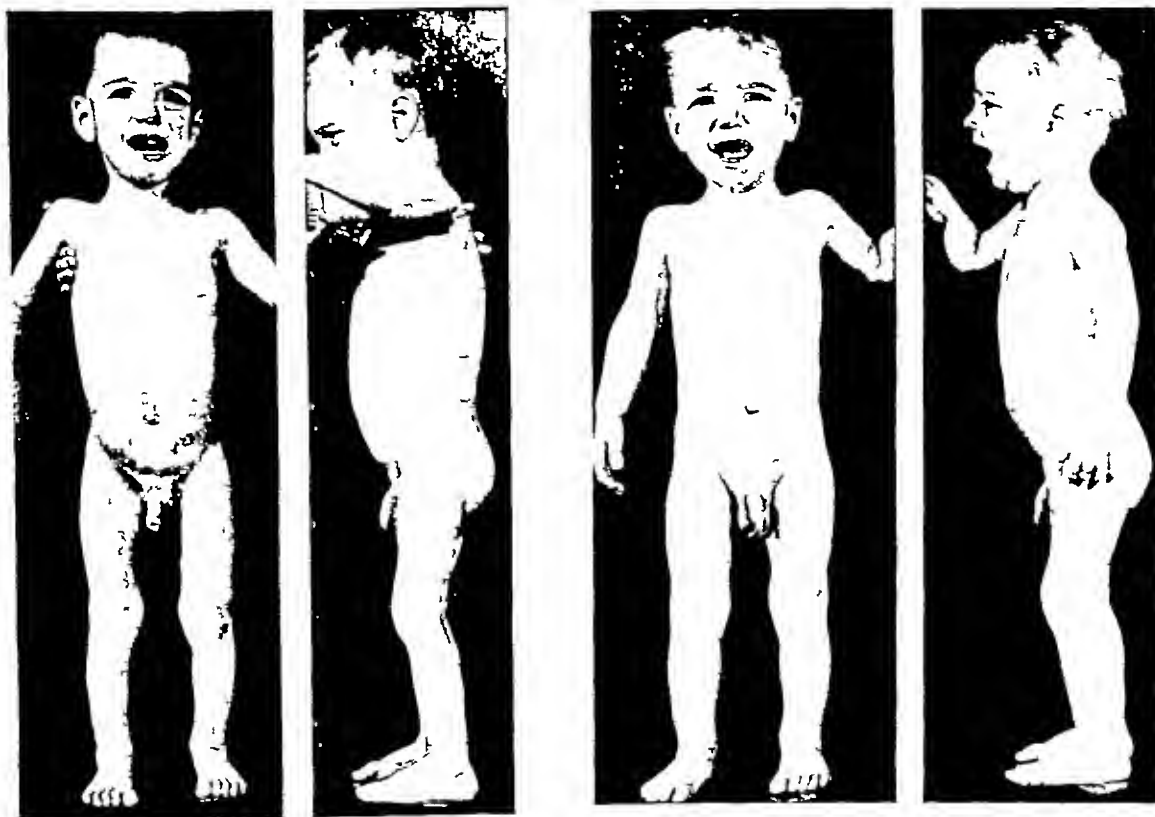


FIGURE 4 Photographs of Patient in Case 19 Taken at the Start of Aureomycin Therapy (Left), and after Four Weeks of 125 mg Twice Daily (Right)

Note the improvement in nutrition and general appearance. The patient gained 4 pounds in four weeks.

phenomena that have been observed repeatedly during prolonged penicillin or streptomycin therapy.

SUMMARY

Aureomycin is effective in the management of the pulmonary involvement in pancreatic fibrosis.

Thirty-five patients treated with different oral doses were followed for periods varying up to four and a half months. The minimal effective dose ranged from 20 to 30 mg per kilogram of body weight given in one or two divided doses a day.

The response was good to excellent in 31 of the 35 cases. This was characterized by disappearance

Staphylococcus aureus was isolated from the nasopharynx of all patients included in this series. The clinical improvement was independent of the bacteriologic findings as determined by study of the nasopharyngeal flora. The in vitro sensitivity of the *Staph aureus* isolated from these patients was determined for penicillin, streptomycin and aureomycin. The majority of strains were relatively more sensitive to aureomycin than to either of the other two antibiotics. The *Staph aureus* isolated from 7 patients during aureomycin therapy showed an apparent increase in resistance ranging from fourfold to thirty-two-fold.

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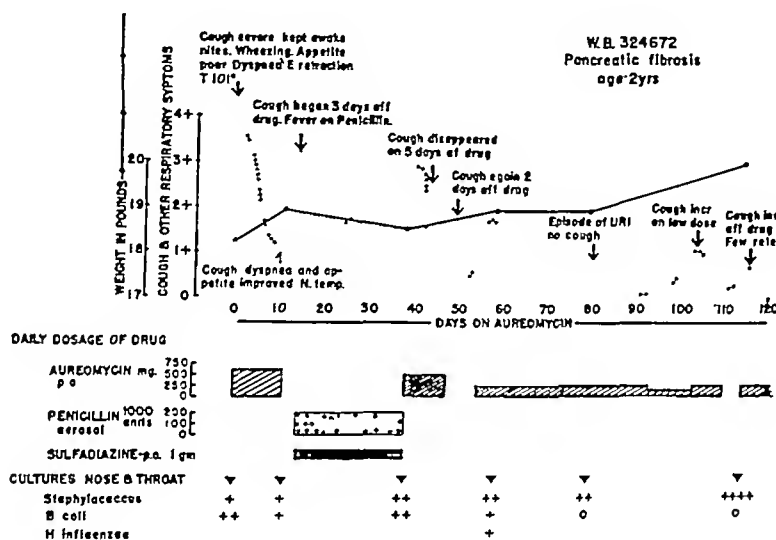


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The development of bacterial resistance to aureomycin has not yet been definitely established, although observations on 7 of the patients in this series suggest that resistance can be acquired after

POSTERIOR TUBERCULOUS SINUSES OF VERTEBRAL ORIGIN*

Wound Revision and Closure with Streptomycin Permitting Early Spinal Fusion

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BEFORE the advent of streptomycin, half the patients having sinuses associated with Pott's disease died. Many procedures were devised and advocated for the control of tuberculous abscesses and sinuses but were uniformly characterized by poor therapeutic response. Aspiration of abscesses and excision of sinuses were followed by recurrence in about 60 per cent of the cases.¹⁻⁹ When such foci of soft-tissue infection presented near the site of tuberculous spondylitis, it was rarely possible to perform spinal fusion without considerable risk to the patient. Usually, in the face of this common complication, all thought of spinal fusion was abandoned. The only alternative was a prolonged and uncertain program of rigid immobilization, the patient being subjected to a variety of physical and chemical agents in an effort to control the tuberculous sinus.

Developments of recent years have greatly improved the outlook of the patient with tuberculous spondylitis. Spinal fusion continues to be the most effective method for control of the vertebral infection, but streptomycin therapy has proved extremely important in the control of the frequently associated infection of soft tissues.¹⁰⁻¹⁴ We are concerned in this study with the posterior tuberculous abscess or sinus complicating Pott's disease, which interferes, by threat of contamination, with the early, definitive care of the underlying vertebral disease. Prompt and effective relief of such posterior foci permits fusion of the spine and rehabilitation of the patient in a period often measured in terms of months rather than years.

Streptomycin will heal most tuberculous sinuses without adjunctive surgical measures, unless drug fastness has developed. However, such treatment is usually prolonged. Twelve of 15 sinuses in Hinchshaw's¹⁰ series closed without recurrence but the duration of treatment recommended was three to four months.

When Brock¹¹ used streptomycin and adequate drainage, 59 of 60 sinuses closed. Seventy per cent of these sinuses required ten to twenty weeks of drug administration to heal. In our clinic this regime

was followed with similar results, but we have found that the period required for healing by second intention with streptomycin may be reduced by surgical closure after adequate wound revision. Our results on secondary and primary closure of the excised tuberculous abscess or sinus with streptomycin therapy have been reported elsewhere.¹⁴

Since our previous report we have confirmed the value of this mode of management, and a much larger series of cases is available for clinical evaluation. In 2 out of 7 cases in which wound revision and primary closure was undertaken, reformation of an abscess under the firmly healed wound occurred. When a period of continuous decompression following débridement was allowed (from two to six weeks) before wound closure was undertaken, only 2 out of 26 cases presented recurrence of a sinus in the healed revision wound. One of these closed before completion of the first course of streptomycin, whereas the other, which was more profusely draining, closed during a second course of streptomycin given for another indication. Both have remained firmly healed. Thus, delayed closure is found, in general, to be the more effective procedure. The chronic, meagerly draining sinus, small in total extent, may be closed by excision and primary suture. When rapid reaccumulation of pus or excessive drainage presents clinically, adequate débridement and a period of continuous decompression are necessary before revision and secondary closure of the wound.

The effectiveness of streptomycin in the treatment of tuberculous sinuses has been improved by the observation of certain surgical principles. These principles are as follows: *superficial encapsulated tuberculous pus must be adequately drained; the tuberculous sinus must be widely deroofed; tuberculous granulation and fibrous tissue must be removed; and extravertebral necrotic bone and cartilage must be removed.*

GENERAL INDICATIONS FOR STREPTOMYCIN THERAPY

Management of the posterior tuberculous abscess or sinus by surgical measures and adjunctive streptomycin therapy varies according to the nature and location of the process. Several categories are met with, two or more of which frequently coexist in the same patient. Some of these abscesses and sinuses should be disregarded when spinal fusion is undertaken. Others require a staged surgical

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On June 13 a 10-day course of penicillin was started consisting of 300,000 units a day. Six days later wound revision and secondary closure was performed. The sinus tract was removed surgically as far as the transverse process of the fourth lumbar vertebra. The fascial layers were developed and sutured without drainage. The wound healed firmly. On July 12 streptomycin was discontinued. A two-stage Hibbs spinal fusion was performed on August 27 and October 8. Convalescence was uneventful. The patient was discharged on March 25, 1948, and has remained well during the 17 months since the final operation.

CASE 3 H W K (R.H.V.A.H 19,758), a 32-year-old man, was admitted to the hospital on December 23, 1946, with a tuberculous sinus in the left posterior lumbar region. The eleventh and twelfth dorsal vertebrae showed osteo-mineralization, but the intervening disk was not thin. In addition there was a left tuberculous pleural effusion, and an apparently arrested, minimal lesion in the upper lobe of the right lung. On October 21, 1945, a left lumbar abscess had been drained. Smear, culture and guinea-pig inoculation were all positive for tubercle bacilli. The vertebral lesion had been diagnosed as tuberculous spondylitis, and a Bradford frame had been employed since December 13, 1945.

Lipiodol studies demonstrated that the sinus extended to the level of the disk between the eleventh and twelfth vertebrae, where it angulated forward to end in a small pocket. On March 14, 1947, chest x-ray study disclosed a diffuse haze through all lobes of the lungs, highly suggestive of miliary tuberculosis. By March 28, these granular markings had increased considerably and streptomycin, 20 gm a day, was begun. The clinical response was excellent, and radiologic clearing was demonstrated by serial chest films. Spinal fusion was then considered in an effort to utilize the favorable streptomycin response.

On July 15 the sinus tract was thoroughly debrided, revised and closed primarily without drainage. There had been no decrease in size of the sinus under streptomycin, but the amount of drainage had diminished considerably in recent weeks. Firm wound healing occurred by first intention. The course of streptomycin ended on July 27. The vertebral bodies of the eleventh and twelfth dorsal vertebrae had become more calcified, with considerable restoration of normal trabecular markings. Some anterior bone bridging was noted, and the paravertebral mass had decreased in size.

On August 15, the patient complained of malaise, nausea and headache. Lumbar puncture revealed an elevated spinal-fluid pressure, with 80 cells, predominantly lymphocytes, per cubic millimeter, a protein of 100 mg per 100 cc. and low sugar and chloride values. The fluid was positive for tubercle bacilli on smear of the pellicle and by culture and guinea-pig inoculation. The patient was transferred to the medical service, where a second course of streptomycin, intramuscularly and intrathecally, was begun. He responded well for 3 weeks but then began to fail. Spinal-fluid streptomycin levels ranged from 15 to 194 microgm per cubic centimeter. He died on November 23, 1947. The spinal-fluid organisms had become resistant to over 1000 microgm. of streptomycin per cubic centimeter.

At autopsy, the entire healed tract was carefully excised and studied. It included skin and the portion of the anterior vertebral ligament at the bone bridge. Many sections were studied by our consultant pathologist, Dr Raymond Goodale, and sections were sent to the Army Institute for special investigation. Both reports stated that there was no evidence of tuberculosis.

CASE 4 H G S (R.H.V.A.H 19,735), a 30-year-old man, was admitted to the hospital on April 3, 1947, for streptomycin therapy. He had had pulmonary tuberculosis since June, 1945, and a left artificial pneumothorax had been maintained since October, 1945. Tuberculosis of the left ninth rib had been diagnosed in July, 1946. Tuberculosis of the tenth and eleventh thoracic vertebrae, with a right lumbar abscess, was discovered in September, 1946. In February, 1947, a spinal fusion was performed, tibial grafts with nut-and-bolt fixation being used. Several weeks after operation the wound broke down and a soft mass appeared over the left iliac region. On admission the upper half of the dorsal spinal-fusion wound was separated and under-

mined, draining a moderate amount of tuberculous pus. There were rapidly reaccumulating, bilateral lumbar abscesses, which undermined the full thickness of the skin across the back.

X-ray study of the chest on admission showed a left pneumothorax and a pleural haze over the apex of the upper lobe of the right lung. Spinal films disclosed narrowing and irregularity of the disk between the tenth and eleventh dorsal vertebrae, the body of the former was irregularly mottled. There was a 12.5-cm., dense, intact bone graft to the left of the spinous processes of the eighth to twelfth dorsal vertebrae, and to the right there were two graft fragments secured by nut-and-bolt fixation. The right psoas shadow was not seen. There was an area of cyst-like rarefaction lateral to the upper angle of the left sacroiliac joint.

Drainage of the wound became slight, but smears and cultures of the wound and the lumbar abscesses were positive for acid-fast bacilli. No connection could be demonstrated between the wound and the lower lumbar abscesses. A 60-day course of streptomycin, 10 gm. a day, was begun on May 14. Two days later the wound was explored, excised and extended. The nut and bolt were easily movable and the right-caudal-graft fragment was loose and roughened. These were removed. The wound was closed without drainage and healed by first intention. On May 26 the right psoas abscess was widely drained, and the undermining symmetric lumbar collections of pus were counterdrained dependently. In all, over 1500 cc. of pus was removed. Revision and secondary closure was performed on June 18. All wounds remained firmly healed.

On August 12 films of the spine showed less mottling and some recalcification of the tenth dorsal vertebra. The paravertebral bulge was considerably less marked. The bone cyst in the left ilium was unchanged. The patient became ambulatory in a Taylor back brace.

On October 25, splenectomy was performed for acute, severe, idiopathic thrombocytopenic purpura. The patient died thirty-six hours postoperatively with a platelet-count rise to only 28,000. No accessory spleen was noted at operation. Permission for autopsy was not granted.

CASE 5 A. R. (R.H.V.A.H 20,155), a 50-year-old man with tuberculous spondylitis of the seventh, eighth and ninth thoracic vertebrae had had a spinal fusion of the sixth to tenth dorsal vertebrae performed in another hospital in June, 1944. He was discharged in January, 1945. He was next hospitalized in October, 1947, for a large fluctuant mass in the right costovertebral region. This mass was drained, and 800 cc. of tuberculous pus was recovered.

In November the patient was transferred to this hospital. He was seriously ill and had suffered a recent 15-lb weight loss. Spinal roentgenograms showed extension of the disease above and below the fusion area and a large paravertebral mass in the posterior mediastinal compartment. Exploration of the fused area and extension of the spinal fusion were contraindicated by the presence of the nearby draining sinus.

Streptomycin, 10 gm a day, was started on December 15, and the sinus was debrided and the abscess deroofed. Three weeks later the wound was revised and secondarily closed. On February 11, 1948 the fusion wound was explored, and a caudal extension of fusion from the eleventh dorsal to the twelfth lumbar vertebra was performed. There was no pseudarthrosis. Immediately after operation the patient became markedly depressed and unco-operative, vehemently resisting food and attempts at intravenous and gavage therapy. The fusion wound dehisced on the 14th postoperative day, and the sinus wound opened and began to drain 5 days later. Cultures were negative for pyogens and tubercle bacilli. With recovery of his mental status and under vigorous nutritional replacement therapy, the wounds healed rapidly. Pressure symptoms from his large paravertebral mediastinal mass became severe, requiring frequent aspirations. Streptomycin was discontinued on April 3.

On June 29, both twelfth ribs were removed because of tuberculous involvement. On September 15 the fusion was extended upward from the sixth to the fourth dorsal vertebra and a second course of streptomycin, 10 gm a day, for 42 days was initiated. With the fusion completed and because of an increase in the width of the paravertebral,

program geared to the effective zone of streptomycin therapy. It should be emphasized that the goal is the early fusion of a tuberculous spine.

The *paravertebral tuberculous abscess* under the anterior longitudinal ligament offers no contraindication to spinal fusion, nor does it of itself constitute an indication for streptomycin therapy except when spinal-cord compression complicates the problem. The tuberculous paravertebral mass frequently decreased in size under streptomycin therapy (Cases 3 and 4), so that streptomycin is indicated when signs of spinal-cord compression exist. Conversely, absence of clinical response to an initial course of streptomycin in the presence of a highly suspicious vertebral lesion and paravertebral mass, with signs of spinal-cord compression, suggests a nontuberculous etiology.* Less serious pressure manifestations of the space-occupying mass are easily relieved by repeated aspirations, without the use of streptomycin, until fusion is completed. Because of the prolonged drainage that follows costotransversectomy, even under months of streptomycin therapy in 2-gm daily doses,¹⁵ this procedure should be delayed, if possible, until the spinal fusion is completed (as in Case 5).

The *deep, burrowing extension abscess* (psoas and so forth) and its more superficial sequelae, which do not point or drain posteriorly, offer no contraindication to spinal fusion. This applies only so far as these infected zones do not present in the projected area of spinal fusion and are, therefore, no hazard from the standpoint of wound contamination.

The *posterior tuberculous sinus and the subcutaneous abscess with marked thinning of the skin, close to the proposed operative area*, have been established as contraindications to spinal fusion. When the tuberculous sinus is the entire and major problem, its management by secondary healing or surgical closure under streptomycin is elective. However, when the sinus is associated with Pott's disease and its proximity contraindicates required spinal fusion, indefinite delay of fusion is avoided by surgical closure of the sinus under streptomycin therapy. The major surgical procedure can then be performed in the safest zone of streptomycin therapy.

CASE REPORTS

This study includes 6 cases of tuberculous spondylitis in which spinal fusion was desirable. In each of these patients fusion was contraindicated by posterior, superficial tuberculous abscesses or sinuses immediately adjacent to the operative field. Two of the foci treated were situated in the posterior midline and the remaining sites ranged from 3 to

12 cm from the midline, with an average distance of 4 cm.

CASE 1 J W M (R H V A H 19,208), a 28-year-old man, was admitted to the hospital on June 20, 1946, with a diagnosis of bilateral pulmonary tuberculosis, moderately advanced.

A roentgenogram of the chest revealed bilateral apical infiltrations. The sputum was normal. Serial films showed progressive clearing and contraction of the apical disease during the next 3 months. In September the patient complained of pain in the right hip. Roentgenograms of the right hip were normal but the lumbar spine showed decalcification and erosion of the anterior surface of the body of the first and the upper border of the second lumbar vertebra, with irregularity and thinning of the intervertebral disk. A presumptive diagnosis of tuberculous spondylitis was made, and the patient was treated by bed rest and Taylor back brace.

In January, 1947, roentgenograms of the spine showed increased destruction of the first and second lumbar vertebrae and beginning involvement of the twelfth thoracic vertebra. The right psoas shadow was obliterated by a mass, presumably a psoas abscess. A 4-cm mass could be palpated in the right lumbar region. The mass rapidly increased to about 15 cm in diameter, undermined across the midline, and pointed above the right iliac crest. It was acutely tender. Frequent aspirations yielded tuberculous pus, and two draining sinuses developed.

On March 4 intramuscular injection of streptomycin was begun, the dosage being 20 gm a day. On the following day the right-psoas-muscle abscess was drained, and 1200 cc of green, creamy pus was recovered. The abscess occupied a space between the peritoneum and the lumbodorsal fascia, extending from the right tenth rib into the true pelvis. It had dissected to the left paravertebral region, superficially through Petit's triangle, and had undermined to the right anterior superior iliac spine. The right quadratus lumborum and psoas muscles were almost totally destroyed. A counter incision was used to drain a daughter abscess over the right posterior superior iliac spine.

During the next 2 months the small daughter abscess and its sinus tract closed, and the superficial undermining area across the midline healed solidly. On May 10, a 12-day course of penicillin was started, consisting of 300,000 units a day. Six days later the wound was revised, the sinus tract and abscess being partially excised, and was closed without drainage. Five weeks later a Hibbs spinal fusion was done from the tenth thoracic to the fourth lumbar vertebra. The fusion mass was supplemented by bone chips taken from the left ilium. Streptomycin was discontinued on July 22, after 140 days of administration. The secondarily closed sinus and the spinal fusion incision have remained solidly healed. The patient was discharged in December and has remained well during the 20 months since his last operation.

CASE 2 W J M (R H V A H 19,385), a 22-year-old man, was admitted to the hospital on September 11, 1946, with a diagnosis of Pott's disease of the fourth and fifth lumbar vertebrae, and left psoas abscess.

A roentgenogram of the chest revealed bilateral apical infiltration. The sputum was normal. Roentgenograms of the spine showed degenerative changes of the fourth and fifth lumbar vertebrae and a left paravertebral mass. A fluctuant, nontender, slightly warm mass, measuring 15 by 5 cm, was felt in the left lumbar region. This mass was centered over the left iliac crest and extended medially across the lumbar spine. The skin overlying the paraspinal region of the mass was thin.

On October 9 a diagnostic aspiration of the left psoas abscess was performed, after which the abscess ruptured spontaneously and began to drain thick, caseous tuberculous pus. Iodized oil injected into the sinus revealed a tract directed anteromedially, not quite reaching the fourth lumbar interspace.

On March 4, 1947, intramuscular injection of streptomycin, 20 gm daily, was begun. On the following day, debridement of the sinus was performed, and considerable diseased tissue was removed. The wound was packed loosely with iodoform gauze.

*G E W Jr (R H V A H 20,430) a 25-year-old man with progressing paraplegia associated with collapse of the tenth dorsal vertebra and a small paravertebral mass was transferred to this hospital with a diagnosis of tuberculous spondylitis after having been in two teaching hospitals. Two diagnostic aspirations of the mass yielded only blood. There was no clinical response to a 3-gm. course of streptomycin. Laminectomy decompression was then performed and biopsy of the involved vertebra revealed a primary malignant capillary hemangioendothelioma.

may occur with astonishing suddenness and is probably irreversible. We do not yet have statistically significant figures on resistance studies in patients exhibiting active involvement of several bodily systems, such as pulmonary, skeletal and genitourinary, who have received streptomycin therapy. Until such data are available, the emergence of resistant organisms from any source in a given patient must be presumed to mean that similar resistance does, or will before long, exist in organisms in other foci within the same person.¹⁷ Tuberculosis is a notoriously recurring disease involving many systems of the body. In the majority of cases, a brief course of streptomycin (measured in total grams) leaves one with a still potent agent for the treatment of unlooked-for complications in the same system or subsequently arising in other systems.

In an attempt to overcome these problems we have added wound revision and primary or secondary closure of the sinus to obtain a clean operative field through which early spinal fusion can be performed. Internal immobilization of the tuberculous vertebrae is accomplished with minimal delay and early in the course of streptomycin therapy. This immobilization will also accelerate healing of the secondary soft-tissue tuberculosis and probably reduce the incidence of sinus recurrence. Furthermore, preliminary study of non-orthopedic tuberculous sinuses suggests that surgical closure reduces the amount of streptomycin required for healing. With primary and secondary surgical closure of tuberculous sinuses, as little as five weeks of streptomycin therapy has sufficed.¹⁴

Recurrence of the sinus in some cases is likely and is an indication of continued activity of the tuberculous infection. In such cases a more intensive course of streptomycin may be required, but clinical judgment should be exercised if the presence of tuberculosis in extraskeletal systems presents other potentially major surgical problems. Maintaining a streptomycin-sensitive organism would then outweigh in importance the recurrence of a tuberculous sinus, particularly if the orthopedic operative problem had been solved. A patient now under observation illustrates this problem. Spinal fusion was performed in 1946 without the use of streptomycin therapy. In mid-1948 a tuberculous lumbar abscess, which drained spontaneously, developed. Roentgenographic examination showed the vertebral lesion to be in a healing phase. There was no extension of disease, and the fusion appeared solid. Observation over a period of months should enable us to decide whether or not further fusion is indicated. Until such a decision is made streptomycin will be withheld, and no surgical treatment of the sinus will be undertaken. If the sinus proves to be the entire problem, it can be readily managed as outlined above.

The ideal management of the problems presented in this study is often not possible. Long courses

of streptomycin were given in the earlier cases because of inexperience, and in the later cases because we had extended our indications for spinal fusion. The experience gained has served to focus our attention more firmly on the conservation of streptomycin through judicious application of cardinal surgical principles initiated at the optimum time. In the favorable case, a short course of streptomycin may well result in a firmly healed posterior tuberculous sinus and fusion wound. In the unfavorable case the indications for spinal fusion may be extended.

SUMMARY

A plan of management for the posterior tuberculous sinus of vertebral origin is described. Streptomycin is employed in a minimal total dosage through the application of established surgical principles, permitting spinal fusion to be performed early, in the safest zone of streptomycin treatment.

In the good-risk patient with a meagerly draining posterior sinus, excision and immediate closure under streptomycin protection result in a firmly healed wound. Spinal fusion may then be carried out early without danger of wound contamination.

In the good-risk patient with a copiously draining posterior sinus, adequate debridement and continuous decompression over a period of days are necessary. Subsequent wound revision and secondary closure under streptomycin therapy result in a firmly healed wound. Spinal fusion is thus but slightly delayed.

In the poor-risk patient with a posterior tuberculous sinus of vertebral origin, the unrestricted use of streptomycin may be necessary, but the plan of management permits spinal fusion early in the course of streptomycin therapy.

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mass, a right costotransversectomy through the ninth and tenth ribs was done on November 15, draining the mediastinal abscess, with marked symptomatic relief. The patient became ambulatory on November 23. Both fusion wounds have remained firmly healed, and the mediastinotomy drainage has gradually diminished.

CASE 6 J L D (RHVAH 18,749), a 23-year-old man, was first hospitalized in January, 1945. A right artificial pneumothorax was attempted for active pulmonary tuberculosis. It was abandoned in May because of adhesions, and in July of that year the right phrenic nerve was crushed and artificial pneumoperitoneum begun.

He was transferred to this hospital on November 25. X-ray films of the chest revealed fibrosis and mottled infiltrations throughout all lobes of both lungs, with honeycombing in the upper lobe of the right lung. Examination of the sputum was negative on admission but became positive in May, 1946. A left pneumothorax was induced on July 1, and was satisfactory.

The first major surgical procedure performed on this patient was a right extrapleural pneumothorax on July 29, 1947, under streptomycin protection, 1.0 gm a day for 42 days. Three months later a right lumbar abscess developed. Repeated aspirations were negative for pyogens, fungi and acid-fast bacilli. The vertebral origin of this abscess could not be ascertained. Because of sinus-tract formation, a wide operative drainage was done on November 13. The right transverse processes of the lower lumbar vertebrae were found to be bare and spongy. Biopsy of the abscess wall showed tuberculosis.

By April 8, 1948, serial x-ray films revealed that the disk between the sixth lumbar and the first sacral vertebra was thin and showed erosion of the anterior inferior border of the sixth lumbar vertebra. A left anterior suprainguinal abscess formed, draining spontaneously after repeated aspirations but yielding negative cultures.

On April 15 the second course of streptomycin, 1.0 gm daily for 42 days, was begun. On April 21, secondary closure of the right posterior sinus was performed. The wound healed firmly. The anterior sinus offered no hazard of wound contamination to spinal fusion and was therefore disregarded. It healed spontaneously 20 days after completion of the second course of streptomycin. A Hibbs fusion of the fourth, fifth and sixth lumbar to first sacral vertebra was performed on May 12. Convalescence was uneventful. The patient became ambulatory with a Taylor back brace on August 11. He is asymptomatic, with a stable fusion, firmly healed wounds, right extrapleural pneumothorax, left intrapleural pneumothorax and a normal sputum since February 10.

GENERAL PROCEDURE

Bacteriologic and anatomic studies must precede streptomycin therapy in the surgical treatment of tuberculous abscesses and sinuses. The tuberculous nature of an abscess or sinus is established by diagnostic smear and culture, guinea-pig inoculation or biopsy. It should be stressed that an adequate specimen must be sent to the bacteriologist. Streptomycin-sensitivity studies are carried out. Radiopaque oil is frequently helpful in outlining the extent of the pathologic process.

The optimal conditions for wound healing are obtained by adequate hydration, high-protein and high-caloric diet, supplementary vitamins and the correction of anemia.

Streptomycin, 0.5 gm twice a day, and penicillin, 300,000 units daily, are given intramuscularly. Within three to seven days, the initial operation is conducted under general anesthesia. If the process is an *abscess*, it is incised and drained dependently. If the process is a *sinus*, its ramifications are derooft. In either event, the tuberculous granulation and fibrous tissue is removed. Lo-

calized pockets of purulent material are counter-drained if necessary. The open wound is packed loosely with iodoform gauze. The pack is removed in forty-eight hours and replaced by saline dressings. These dressings are changed daily, and the wound is irrigated.

Seven days after the first operation, the wound is revised and secondarily closed. The basic surgical routine is as follows: under general anesthesia, the skin margins are cut a few millimeters from the edge of the wound. The sinus wall is excised. The wound is thoroughly lavaged with saline. After a change of instruments, drapes, gowns and gloves, the fascial planes and subcutaneous tissues are developed into layers and closed with interrupted sutures of fine chromic catgut. An attempt is made to obliterate dead space. The skin is closed with fine-silk sutures without drainage. A pressure dressing is applied. Streptomycin is given until healing of the sinus appears complete.

Inasmuch as organism resistance is in direct proportion to the amount of streptomycin used, every effort should be made to keep the total dosage at a minimum. In the special problem of posterior tuberculous sinuses the optimum dosage of 1.0 gm of streptomycin daily may be reserved for the immediate operative period when closure of the sinus is accomplished. To protect the healed, surgically closed sinus wound, streptomycin should be continued at a reduced dosage schedule, until spinal fusion is performed, usually an interval of two or three weeks. The minimal safe but effective dose of streptomycin in this interval has not been established and probably varies with the activity of the underlying osseous lesion. Our present trend is toward the use of 1.0 gm of streptomycin every second or third day.

DISCUSSION

Posterior tuberculous sinuses associated with tuberculosis of the spine may present a specific problem. Spinal fusion frequently is not performed because of the presence of these superficial abscesses and sinuses in the projected operative area. Even with streptomycin and adequate drainage, spinal fusion is delayed because of the time required for healing by secondary intention. In addition, prolonged administration of streptomycin may be accompanied by drug toxicity and bacillary resistance.

Streptomycin is effective in the treatment of the early acute exudative lesion of tuberculosis caused by a sensitive organism, and hence is of value in operative procedures in which tuberculous dissemination may occur.¹⁶ Streptomycin resistance of tubercle bacilli occurs initially in a few untreated cases, and as early as the fourth week in organisms initially sensitive to (inhibited by) 0.5 microgm of streptomycin per cubic centimeter. Resistance is proportional to the total accumulated dose. It

and spleen had developed, the patient died with minimal and terminal involvement of the lungs

CASE 1 A 51-year-old man noticed, over a period of 4 months, malaise, low-grade fever, anorexia, loss of weight and periodic chilly sensations without frank chills

Physical examination showed a slight, general enlargement of all peripheral lymph nodes, and the ankles were moderately swollen and definitely red. No abnormalities were detected in the examination of the heart and lungs, but the spleen was palpable. A roentgenogram of the chest showed the widening of the mediastinum and enlargement of the hilar lymph nodes, with some diffuse peribronchial thickening (Fig 1)

The temperature was 103°F, the pulse 104, and the respirations 22, the blood pressure was 126/70

The red-cell count was 3,260,000, with a hemoglobin of 9 gm (58 per cent), and the white-cell count 5640, with 60

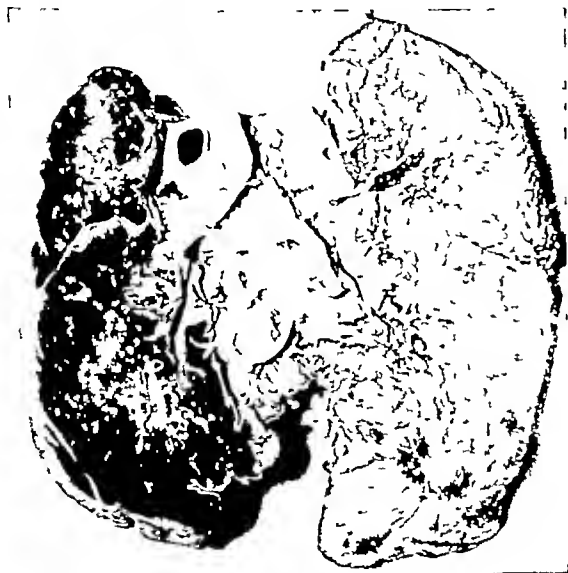


FIGURE 2 Gross Specimen at Autopsy, Showing Caseous Lymph Nodes and Terminal Miliary Lesions in the Lungs (Case 1)

per cent neutrophils, 12 per cent large lymphocytes, 24 per cent small lymphocytes and 4 per cent monocytes. Studies of the bone marrow showed a depression of all hemopoietic elements but no abnormal cells

A tentative diagnosis of inoperable bronchiogenic carcinoma or lymphoma of the lymphosarcoma type was followed by a therapeutic trial of 1500 r

The hilar infiltration increased slowly over a 10-week period. The temperature remained between 103 and 104°F for 8 weeks and then became remittent for the last 2 weeks. A noma-like lesion appeared on the right cheek during the 5th week of hospitalization. Final examination of the blood on the day before death showed a red-cell count of 2,630,000, with a hemoglobin of 7 gm (49 per cent), and a white-cell count of 2240, with 21 per cent segmented neutrophils, 33 per cent stab forms, 27 per cent juvenile forms, 12 per cent large lymphocytes and 6 per cent small lymphocytes

Autopsy revealed a primary tuberculous pneumonia in the lower lobe of the right lung, caseation of the mediastinal lymph nodes (Fig 2), generalized tuberculosis of the lungs, liver and spleen (Fig 3), serofibrinous tuberculous pleurisy and secondary fusospirochetal gangrene of the right cheek

In the following case the onset of primary progressive tuberculosis was insidious, with gradual

involvement of the lymph nodes and spleen, suggesting the diagnosis of a lymphoma of the Hodgkin type

CASE 2 A 30-year-old man moved from a rural area into an industrial center. About 6 months later malaise, a low-grade fever and a slight generalized lymph-node enlargement developed. A roentgenogram of the chest showed a definite widening of the mediastinum, and a diagnosis of lymphoma of the Hodgkin type was made. A biopsy of a peripheral lymph node showed a granulomatous reaction and definite tubercle formation. The clinicians interpreted the finding of tubercles in the lymph node as incidental and reaffirmed the diagnosis of lymphoma

The course of the disease, which was insidious in its beginning, now became more fulminating. There was marked malaise, anorexia, a spiking temperature and loss of weight. The patient became comatose and died 1 week later. The duration of the acute phase of the disease was a little over 8 weeks

Autopsy showed the presence of large caseous hilar lymph nodes (Fig 4), an enlarged, infected spleen, tuberculous meningitis and terminal miliary tuberculosis

The following case, an example of a chronic, progressive, primary tuberculosis with destructive lesions of the vertebrae, was incorrectly diagnosed as lymphoma, metastatic neoplasms or mycotic infection

CASE 3 A 40-year-old woman suddenly became ill 6 weeks before her first admission with chills, malaise and a temperature of 103 to 104°F. After penicillin therapy for 2 weeks and streptomycin for 1 week, the fever was reduced but not eliminated

On admission in October, 1946 the patient apparently was chronically ill, with slight tenderness in the epigastrium



FIGURE 3 Photograph of the Spleen in Case 1
The large white areas are tuberculous abscesses containing numerous tubercle bacilli

and the right upper quadrant. A roentgenogram of the chest showed a mass in the superior portion of the right hilus and another, smaller mass in the left hilar region

Examination of the blood revealed a red-cell count of 3,650,000, with a hemoglobin of 10 gm (69 per cent), and a white-cell count of 8500, with 75 per cent segmented neutrophils, 2 per cent eosinophils, 3 per cent monocytes and 20 per cent small lymphocytes. Studies of the bone marrow showed no abnormalities

PROGRESSIVE PRIMARY TUBERCULOSIS IN THE ADULT AND ITS DIFFERENTIATION FROM LYMPHOMAS AND MYCOTIC INFECTIONS*

DAVID T. SMITH, M.D.†

DURHAM, NORTH CAROLINA

THE death rate from tuberculosis in the United States has decreased from 200 per 100,000 in 1900 to approximately 30 in 1948. The present population is intermittently rather than constantly exposed to tubercle bacilli, consequently, an ever-increasing number of adults are found to be tuberculin negative.

Although conclusive statistical data are lacking, apparently the primary infection in the adult is predominantly an asymptomatic process. When

Occasionally, in the adult there is a steady relentless progression of the disease until all the internal organs are infected and death ensues.

In 5000 consecutive autopsies at the Duke Hospital, Durham, North Carolina the diagnosis of disseminated tuberculosis was recorded 40 times in adult patients. A review of the protocols shows that a number were examples of chronic fibrocaseous tuberculosis with terminal dissemination. In other cases the initial infection may have been a primary one, but the course of the disease and even the autopsy findings were indistinguishable from those of the ordinary chronic "reinfection" type of tuberculosis. After these questionable cases had been discarded a residue of 20 remained in which the extent and character of the lymphatic involvement was characteristic of a primary infection. There were 11 males and 9 females in this group, varying in age from eighteen to sixty. Five patients were white, and 15 were Negroes.

The relative frequency of this type of tuberculosis is emphasized by the observations that in the same series of 5000 autopsies, there were only 20 lymphomas of the Hodgkin type, 4 cases of Addison's disease and 4 of hemochromatosis.

It must be confessed that the clinical diagnosis in these cases of progressive tuberculosis was usually incorrect. Except for the 5 that terminated with a tuberculous meningitis, only 1 case was correctly diagnosed ante mortem.

Perhaps the most important point to remember in making the diagnosis is that primary disseminated tuberculosis can occur in the adult as well as in the child. With the possibility of tuberculosis in mind, one then looks for local and general lymphatic involvement, including an enlargement of the spleen. Whereas the hilar lymph nodes are frequently enlarged, the lungs show little if any infection until the terminal stage, and the sputum, if present, is almost invariably negative for tubercle bacilli.

The tuberculin test is positive in the early weeks and months of the disease but may disappear as the patient becomes exhausted. The white-cell count may be either elevated or depressed, but there is almost always a specific decrease in the small lymphocytes.

Some of the variations in individual cases are illustrated in the following case reports.

CASE REPORTS

In the following case after a high, continuous fever with progressive enlargement of lymph nodes



FIGURE 1 Roentgenogram of the Chest, Showing Widened Mediastinum and Enlarged Hilar Lymph Nodes in Case 1

lesions do appear in the lungs a few months after the conversion of a negative to a positive tuberculin test, they usually have the roentgenographic appearance of an ordinary, chronic type of adult or reinfection tuberculosis and follow a similar clinical evolution.^{1-5†}

*Presented at a meeting of the Suffolk District Medical Society, Boston, March 10, 1949.

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†Professor of bacteriology and associate professor of medicine, Duke University School of Medicine.

‡The clinical, roentgenographic and pathological aspects of experimental primary and reinfection tuberculosis in the rabbit have been studied in detail by Burke.^{6,7}

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Small doses of x-ray, followed by large doses, were applied over the hilar masses. The masses slowly disappeared, and 3 months after admission she was discharged afebrile and apparently improved.

During the next 3 months at home some lymph nodes appeared in the neck but disappeared spontaneously. The discomfort in the right upper quadrant continued, and a

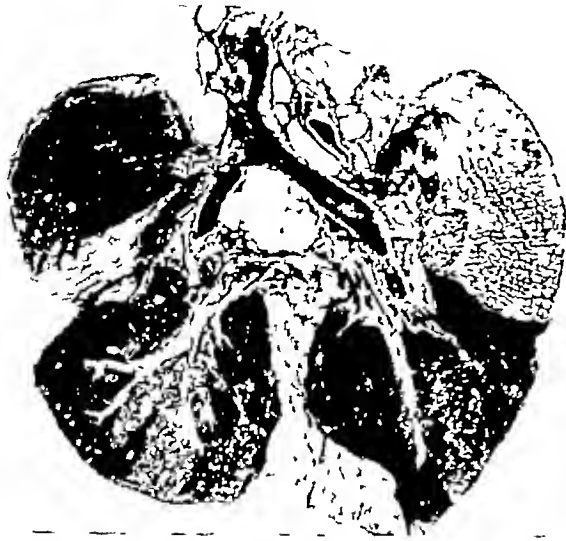


FIGURE 4 Gross Specimen at Autopsy in Case 2, Showing Large Caseous Hilar and Peritracheal Lymph Nodes

new area of pain appeared beneath the lower third of the sternum.

Barium studies during the second admission in March, 1947, showed indentations in the esophagus suggestive of pressure by lymph nodes. She received 1250 r over this area and was discharged.

A low-grade fever persisted from March to July, and then a slight nonproductive cough, hoarseness and some difficulty in swallowing developed.

During the third admission in July, 1947, an x-ray film of the spine showed slight narrowing between the fifth and sixth cervical vertebrae. An examination of the larynx revealed a paralysis of the right vocal cord. A tuberculin test was performed, for the first time, and found to be positive in a 1:1,000,000 dilution of old tuberculin. Desensitization to tuberculin beginning with a 1:100,000,000 dilution and progressing to 1 cc of 1:1,000,000 was attempted.

The patient returned home, where she received 1 gm of streptomycin daily for 6 weeks. Striking improvement occurred while the streptomycin was being taken and for a few weeks after it was discontinued. She became afebrile, felt quite cheerful and returned to work on a part-time schedule. By November, however, severe pains appeared in the mediastinal region, which required Demerol as often as three times a day.

During the fourth admission, between January 6 and 12, 1948, she seemed quite well and was afebrile, but x-ray study showed a destructive lesion with partial collapse of the fourth thoracic vertebra.

The fifth admission, between January 28 and February 7, was characterized by low-grade fever and bilateral pleuritic pain.

The final admission was on July 15. The patient gave a history of being almost well in March and April followed by fever and vertebral pain in May. Streptomycin treatment for 3 weeks produced a remission, but a relapse soon occurred and streptomycin now was ineffective although continued for an additional 4 weeks.

Physical examination showed the patient to be quite ill, and the abdomen was distended and tympanic. The diaphragm was definitely elevated on the right, and films of the abdomen indicated that both liver and spleen were enlarged. She died on July 25, approximately 2 years after the beginning of her illness.

Autopsy revealed the residue of a primary tuberculous infection in the right upper lobe of the lung, scarred and fibrotic hilar lymph nodes and scarred and partially healed lymph nodes along the esophagus, and in the abdomen at the hilus of the liver. One of these lymph nodes was adherent to the stomach on one side and to the liver on the other. A rupture of this node into the stomach made a pathway for pyogenic organisms, which caused a large nontuberculous abscess in the liver. The destructive lesions in the bodies of the vertebrae were tuberculous and not neoplastic.

In the following case, the primary infection was in the cecum, and the presenting symptom was an appendiceal abscess followed by evidence of aplastic anemia and low-grade intermittent fever. Finally, the development of round lesions in the lungs suggested the diagnosis of neoplasia with pulmonary metastasis.

CASE 4 A 60-year-old man was admitted to the hospital in February, 1940, with a mass in the right lower quadrant. A diagnosis of appendiceal abscess was made and confirmed by operation 2 months later. The patient recovered from the operation but became progressively more anemic and did not respond to iron, liver extracts or multiple blood transfusions.

A filling defect found in the region of the ileocecal valve by barium studies persisted throughout his illness.

The lungs were normal for the first 2 years, but during the last 2 years small, round discrete areas appeared in the chest films. Some of these areas decreased in size, others seemed to change in shape and outline, and new ones appeared from time to time.

The patient had fifteen admissions for aplastic anemia over a 4-year period and finally died in circulatory collapse.

At autopsy tuberculous ulcers were found in the colon. The mesenteric, retroperitoneal and mediastinal lymph nodes

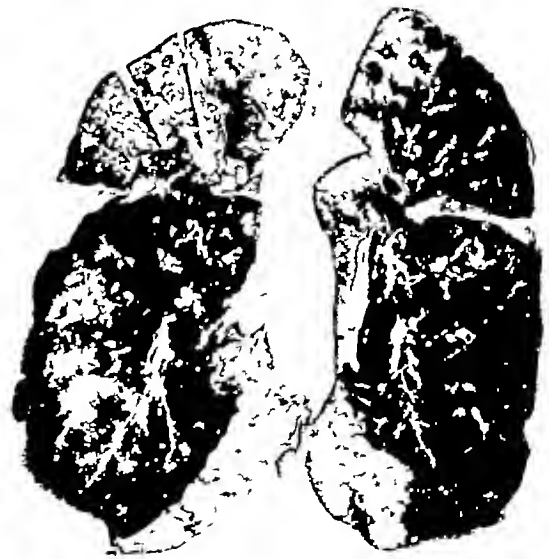


FIGURE 5 Gross Specimen at Autopsy in Case 4, Showing Round Areas of Tuberculous Infiltration Scattered through the Lungs

Apparently, the primary infection was present in the cecum and the hilar lymph nodes were not appreciably enlarged.

were caseous and contained tubercle bacilli. The spots in the lungs were tuberculous lesions (Fig 5). The spleen was enlarged and contained miliary tubercles. The bone marrow from the humerus was essentially normal.

DIFFERENTIAL DIAGNOSIS

The difficulty in differentiating primary progressive tuberculosis and some types of lymphoma is obvious. Moreover, in the past decade, it has been found that certain types of mycotic infections duplicate the clinical picture of progressive tuberculosis almost exactly. Histoplasmosis, coccidioidomycosis, sporotrichosis and South American blastomycosis all have a progressive fatal form characterized by enlargement of the lymph nodes and spleen. They also frequently show destructive lesions of the bones.

SKIN TESTS

Twenty-five years ago tuberculin skin tests were rarely employed in internal medicine because almost the entire adult population was tuberculinized. At the present time, however, there are many areas in this country where less than 50 per cent of the adults have a positive skin test. Except in obviously moribund patients, a negative test to 1 mg of old tuberculin or to the second strength dose of purified protein derivative practically eliminates the possibility of tuberculosis. One need not fear a false-negative test in the early stages of primary tuberculosis because the patient with primary tuberculosis does not develop symptoms until after the skin test becomes positive.

Skin tests with tuberculin-like antigens prepared from fungi are of definite but limited value in diagnosis. Positive skin tests develop quite regularly in persons who have had either a clinical or a subclinical infection with *Coccidioides immitis* or *Histoplasma capsulatum*, therefore, a negative skin test will eliminate the possibility of infection by these organisms unless the patient is in the terminal anergic phase of the disease. When concentrated antigens are injected into highly sensitized guinea pigs, cross reactions can be elicited with coccidioidin, histoplasmin and blastomycin.⁸ This suggests that there is a minimal amount of a common antigen in all three fungi. In the doses commonly used for skin tests, persons with positive skin tests to coccidioidin do not give cross reactions with histoplasmin and blastomycin. However, *Blastomyces dermatitidis* and *H. capsulatum* share a larger amount of a common antigen.⁹ Subjects who have had a subclinical infection with *H. capsulatum* usually react both to histoplasmin and to blastomycin, although in my experience the size of the reaction to blastomycin is always smaller and disappears completely if more dilute antigens are used for the test.

COMPLEMENT FIXATION

In contrast to the skin test, complement-fixing antibodies either do not appear or disappear shortly after a subclinical or mild primary clinical infection with *C. immitis*¹⁰ and *H. capsulatum*.¹¹ However,

in the progressive form of the disease the complement-fixing antibodies are regularly present, and the titer persists even when the anergic phase appears and the skin test becomes negative. Cross complement fixation is not observed between patients having coccidioidomycosis and histoplasmosis. Most patients, however, who fix complement to high titer with histoplasmin antigen also fix complement with the blastomycin antigen, but always at a lower titer.¹¹

The complement-fixation test for tuberculosis is not reliable, but the new agglutination test introduced by Middlebrook and Dubos¹² may prove to be extremely useful in early diagnosis.

BIOPSIES

If an enlarged lymph node is accessible a biopsy usually makes the differential diagnosis. The biopsy is particularly valuable in separating out the cases of sarcoidosis (Boeck's sarcoid) that may have been included with the lymphomas because the tuberculin test was negative.

The biopsy specimen should be cultured for tubercle bacilli and fungi. A culture is essential for the diagnosis of sporotrichosis, since the organisms are almost never seen in sections of human tissues.¹³

CULTURES

All the yeast-like and mold-like fungi will grow on both 1 per cent dextrose agar and on blood agar at either room or incubator temperatures. Since growth may be very slow, the culture should be inspected every few days up to a maximum of thirty days.

SUMMARY

With the rapidly increasing number of persons reaching maturity without becoming infected with tubercle bacilli, a larger number of adults will be found on the general medical wards with progressive primary tuberculosis. These cases resemble quite closely lymphoma of the Hodgkin type, progressive coccidioidomycosis and histoplasmosis, and, to a lesser extent, leukemia, aplastic anemia, metastatic neoplasm and sarcoidosis.

Before the discovery of promizole and streptomycin, the diagnosis of progressive primary tuberculosis was of academic interest only, but now, with a reasonably early diagnosis, some of these patients can be cured.

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HOSPITAL ADMINISTRATION AS A MEDICAL SPECIALTY*

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HOSPITAL administration as a medical specialty seems to be disappearing. The change may be more relative than actual, as able lay administrators become increasingly interested in an expanding profession, but few physicians, it seems, even consider the possibility of hospital administration as a career. What does the specialty offer? Should it be abandoned to trained laymen? In the search for answers to these questions, a brief review of the past history and the present status of hospitals and hospital administration may be of value.

One of the first hospitals of which there is record was founded by Justinian in Rome in 369 A. D. The first known hospital on this continent was established in Mexico by Cortez in 1524. A hundred and twenty years later the Hôtel Dieu was opened in Montreal. The first general hospital in the colonies was the Pennsylvania General Hospital, founded at Philadelphia in 1756. In 1811 the first general hospital in Massachusetts and the third in the United States was founded; it was opened in 1821 and still stands as a tribute to the Reverend John Bartlett and the two physicians, Drs. Charles Jackson and John C. Warren, who were instrumental in its establishment, as well as to the many who since then have added to its fame.

Since its beginnings in this country, the voluntary hospital has been rather an anomaly. It is founded and operated (at a loss) as a charity, it is supported by the time, skill and funds of physicians, individuals, businesses and lately by Community Chests; it is governed by a board of trustees, usually laymen, it often functions not only as a hospital but also as a health center for the area it serves. The hospital has often been referred to as "the physician's workshop." Could one imagine a manufacturer inviting workers into his plant to work for themselves with his equipment and his personnel? In a modified way this is the relation between the physician and at least the smaller hospitals. Although physicians care for service and private patients, the trustees

have the final responsibility for everyone and everything in the hospital. They must hand down the policies by which the hospital operates and are, potentially at least, responsible for the adequate care of every patient, service and private. To execute the details of operation the trustees usually engage an administrator, who in turn supervises the operations of the hospital. He works with the staff to ensure adequate care of patients, to stimulate research and to co-ordinate the multiple aspects of the small city under his guidance. In addition, of course, he is concerned with purchasing and personnel, and may well have the added problems of an educational institution—at least a school of nursing, if not other more advanced medical-teaching programs.

How did this administrator come to be, and what is happening to him? In the early days, when hospitals were operated solely for the poor, a resident physician was usually engaged. His duties were to care for the patients and to administer the institution. It was preferable that he be married in order that his wife might serve as matron and housekeeper. As hospitals enlarged, both the operation of the institution and the care of the patient became much more complex. Gradually a division took place until the administrator was no longer directly responsible for the medical care of the patient. It is only in relatively recent times, however, that administrators have gathered together as a specialty group to establish uniform practices. The American Hospital Association held its fiftieth convention only last year. Thus, it is within the memory of many still living that hospital administration as a specialty and as a career has become known.

In 1933 a group of men meeting in Chicago formed the American College of Hospital Administrators, an organization to "establish high professional standards and to further the education of those in the hospital field." In the last sixteen years this organization has done much to advance the profession.

*Presented at the annual meeting of the Massachusetts Medical Society, Worcester, May 24, 1949.

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Several universities have recently offered courses in hospital administration. The first successful course was established by Dr A G Bachmeyer at the University of Chicago. At present courses are also offered at Yale, Columbia, Washington, Minnesota, Northwestern and other universities. They consist of one year of didactic teaching followed by a year of internship in an approved hospital. Although the instruction is open to physicians, enrollment consists almost exclusively of laymen. Upon successful completion of the course, the student receives a master's degree in hospital administration. In contrast to these formal courses several hospitals have for many years offered to physicians apprenticeships in hospital administration, among these are the Peter Bent Brigham Hospital and the Massachusetts General Hospital.

When a man has completed his schooling or his apprenticeship, or both, he may be chosen by a board of trustees as director of a hospital. He then stands, as the American College of Hospital Administrators has put it, at the helm of the hospital, as others have put it, he is ground between the upper millstone of the trustees and the nether millstone of the staff. Neither description is completely accurate. Given a good board of trustees (and it never ceases to be impressive how loyal and understanding such a group of civic-minded citizens can be), he may if he is a physician, "sit on the sidelines and watch the game," but he often has a better view than the man in the line. What are the disadvantages and the advantages of such a specialty for a physician? A few that come to mind are as follows:

Disadvantages

He is not in business for himself and is subject to dismissal. As in any appointive position, his success (or failure) proceeds more by steps than by the gradual change usual in active practice. Every physician, however, has the same opportunities to succeed or to fail. To be sure, the administrator is working for a small group who have the power to hire and to fire, but his chances of proving his worth to a small group may well be greater than those of a physician to the general population of the city or town where he practices. Given a good board, and most hospitals have them, the hospital administrator will have every chance to show his capabilities and to grow in his chosen specialty. Should his situation for any reason become intolerable, he can usually effect a change without the financial loss entailed in relocating a practice.

His income is limited compared to that of a physician in some other specialty. This is very true, but although the peak may not be so high, he will probably do at least as well in the early years. Taxes being what they are today, this is perhaps better. His income depends upon the

wishes of his trustees as well as his ability, this may be a disadvantage.

He must adjust himself to the personalities of trustees, staff personnel and patients. At times these adjustments may be very difficult, but do not physicians have all of them to some degree no matter what phase of medicine they choose?

He must operate a business. This is probably one of the greatest (if not the greatest) drawbacks for a physician. Most doctors go into medicine, in part at least, because they are idealists and rather shun the business side of life. The administrator must operate a big business — one of the largest in his community. He must operate it as economically as possible, and yet never with thought of profit. If he should operate in the black, he must give thought at once to a reduction in rates, for profit is not a purpose of a voluntary hospital. The multiple, complex problems of staff and personnel relations, wage schedules, purchasing, maintenance and all the others are with him constantly. To be happy in hospital administration a physician must enjoy business life to a certain extent.

He sits on the sidelines and watches the game being played. This, also, is one of the greatest disadvantages. The administrator must be willing to give up active, personal care of patients. He must, although using his knowledge as background, defer to his chiefs of services in matters of medical opinion. This disadvantage is balanced to some considerable extent by the first of the advantages noted below.

Advantages

He has an instrumental share in an enterprise greater than is possible (except for rare instances) in practice. Although he sits on the sidelines he has, throughout his career, a voice in calling the plays, in directing the progress of medicine in the hospital with which he is associated. From the professional side the course that is taken by his hospital during his tenure of office is in his hands to a greater degree than it is in the hands of any other staff member. What he may lose in the individual care of the patient, he gains in the setting of broad, over-all policy.

Community responsibilities. As director of a hospital today the physician, perhaps even as much as the public-health officer, represents to his community the general field of health. He serves on committees and organizations, he speaks to groups. Since he is not in practice he can take a much more active part in this phase of community life without fear of being unethical. As health has joined food, clothing and shelter to become the fourth necessity of life, so it is increasingly important that the story of health services be properly presented to an interested

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MEDICAL PROGRESS

VIRAL INFECTIONS CONTRACTED IN THE LABORATORY*

S EDWARD SULKIN, PH.D.† AND ROBERT M. PIKE, PH.D.‡

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THE increased interest in viral diseases in recent years, particularly in the field of laboratory diagnosis, has stimulated more and more laboratories to undertake work with these agents. Diagnostic procedures that formerly were to be found only in periodicals have now been collected in a single volume by Francis and others¹ who present them in a manner for ready reference for the average worker in the diagnostic laboratory. The availability of antigens² for use in the complement-fixation test makes it possible for any laboratory familiar with this technic to detect an increased antibody titer for a number of viral agents. Because work on viruses gives promise of continuing to expand rapidly, it seemed timely to call attention to the possibility of laboratory infection by reviewing cases that have occurred in various laboratories in the hope that such information would indicate where the greatest need for caution exists. Furthermore, recognition of the causes of such accidents, as far as they are known, may stimulate confidence on the part of those who would otherwise be discouraged from attempting such work.

A number of cases of laboratory infection have been reported in the literature. Early in our survey, however, it became apparent that numerous cases have been observed that have not been reported. Accordingly, an attempt was made to obtain information regarding such cases. The gratifying response to the inquiry on the part of various investigators in this field has added considerable information.†

No exhaustive attempt has been made to survey the situation regarding laboratory infection with organisms other than viruses although it is well known that many such infections have occurred, particularly with the brucella group³⁻⁵ with *Pasteurella tularensis* and *Past. pestis*^{4, 5} with *Bacillus anthracis*,⁶ with the typhoid bacillus⁷ with *Malloomyces mallei*⁸⁻¹⁰ with leptospira^{11, 12} with the borrelia,¹³ with *Treponema pallidum*,¹⁴ with *Coccidioides immitis*¹⁵ and doubtless with the tubercle bacillus and numerous other micro-organisms.¹⁷⁻¹⁸

The hazards involved in work with rickettsias have also been recognized. Virtually all laboratories working with typhus rickettsias have experienced infections among the personnel.^{19, 20} *Rickettsia prowazekii*²¹ and *R. nooseri*^{21, 22} have been responsible for such cases. Vaccination does not, apparently, entirely remove the risk of infection,^{23, 24} but the disease in vaccinated persons tends to be milder^{25, 26} and the incidence of infection is decreased.²¹ Laboratory infections with *R. tsutsugamushi* (*R. nipponica*)²² *R. rickettsi* (*Dermacentrophenus rickettsi*)²³ *R. conorii*²⁴ and *R. quintana*²⁵ have also been reported. The first known human infection with the agent of American Q fever occurred as a laboratory infection.²⁶ Other laboratory cases of Q fever have occurred in Australia²⁷ in the Mediterranean area²⁸ and in this country.²⁹⁻³¹ Even the most recent addition to the Rickettsia group *R. akari*, has been responsible for 2 cases of rickettsialpox in the laboratory.³²

Cases of viral infection that are believed to have been contracted in the laboratory are summarized in the accompanying Table 1 and 2. Those accidentally acquired outside the laboratory, such as the cases of encephalitis among veterinarians reported by Meyer¹³³ and Sulkin¹³⁵ and the case of equine infectious anemia in a person who had had contact with infected horses,¹³⁷ together with the numerous cases of psittacosis^{136, 138} among bird handlers, have not been included. In a few cases as indicated in the tables, there is some doubt that the infection was acquired in the laboratory, but the possibility seemed strong enough to warrant its inclusion. The etiology was proved in most of the cases by one or a combination of the following technics: isolation of the virus, demonstration of a significant rise in neutralizing or complement-fixing antibodies in blood samples obtained during convalescence as compared with those drawn during the early phase of the illness, or demonstration of a significant antibody titer in a single sample of serum in a person who presented a typical clinical course of the illness in question together with evidence of exposure to the viral agent. In cases in which this evidence was lacking, there was little doubt regarding the nature of the infection.

In all 222 cases with 21 deaths have come to our attention. Of the numerous viral agents involved, 5 have accounted for over two thirds of the infections — namely, yellow fever, Rift Valley

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§At the present time a number of viral antigens for use in the complement-fixation test are available commercially.

¶We are indebted to the many workers in the field who contributed the data that made this review possible.

public The hospital director is constantly called upon to perform this civic duty

His income is steady Although he will never amass a fortune—and few doctors do—he is assured of a regular income, regular vacations and often the benefits of sick leave and retirement His income is in many ways more secure than that of his fellow physicians

His contacts are pleasant In this aspect he differs little from the practicing physician

His hours of work are better than those of most physicians He is better able to schedule his time and can usually expect to work a more or less regular week Meetings, often in the evening, and on-call coverage may be somewhat confining, but these, too, can usually be scheduled By and large the physician administrator sees more of his family than the physician in practice does

He has counsel available should he need it The help that the administrator has available from his staff is obvious, in addition, if his board of trustees is a broad, representative body, he can, if he chooses, call upon any of several members for assistance in problems ranging from finance through personnel to workmen's compensation insurance He rarely needs to sail without guidance on uncharted seas The degree to which he may do so usually depends upon the man himself

Are physicians interested in the future of hospitals? They must be, for hospitals are so increasingly intimately connected with the practice of medicine that neither can stand alone If doctors are vitally interested in the future of hospitals, must they not be equally interested in their operation? The administration of the hospitals in this country is being taken over more and more by able lay administrators This is not because medical administrators are so poor, but because they are so few If those with no prior medical experience are recognizing the opportunities of this profession, are physicians not derelict in their duty if they do not bring its opportunities before medical students, interns and residents?

Given other qualities that are equal, it seems logical that since a hospital's prime reason for existence is care of the sick, a man with a medical background should make a better hospital administrator than one without In the interests of the future of hospitals, therefore, and in the interests of medicine as well, it behooves physicians to keep the opportunities of this too often forgotten specialty before themselves and before those who follow them While recognizing the importance of having able laymen in the field of hospital administration, they should reverse the trend of decline of hospital administration as a specialty chosen by physicians The first step in such a program is to present the specialty for consideration to medical students, interns and residents

TABLE 1 (Continued)

Virus	No of Cases	No of Deaths	Probable Source of Infection	Incubation Period	Virus Recovered	Antibodies Demonstrated	Authors
Yellow fever	7	0	Handling of infected laboratory animals	Unknown (6 cases) 2 (1 case)	Yes (4 cases) No (3 cases)	Yes (6 cases) No (1 case)	Theiler ¹⁰² Berry and Kitchen ¹⁰³ Low and Fairly ¹⁰⁴ Dinger ¹⁰⁵ and Dinger et al. ¹⁰⁶
	2	1	Handling of infectious human blood	10	Yes (1 case) No (1 case)	Yes (1 case) Not tested (1 case)	Low and Fairly ¹⁰⁵
	1	1	Autopsy on yellow fever patient	No data	Not tested	Not tested	None ¹⁰⁸
Dengue fever	1	0	Unknown	Unknown	No	No	Rockefeller Foundation*
	1	0	Contamination of conjunctival sac with human virus	10	No	Yes	Melnick et al. ¹⁰⁷ and Sahin ¹⁰⁸
Rift Valley fever	3††	0	Patients performed autopsies on infected lambs	5-6	Yes (2 cases) No (1 case)	Yes	Findlay ¹⁰⁹
	15‡‡	1	Unknown patients worked with virus	Unknown (12 cases) 6 (1 case) 4 (1 case) 7 (1 case)	Yes (14 cases) No (1 case)	Yes (12 cases) Not tested (3 cases)	Schwentker and Rivers ¹¹⁰ Kitchen ¹¹¹ Francis and Magill ¹¹² Magill ¹¹³ Sahin and Blumberg ¹¹⁴ and Smith-hurn ¹¹⁵
	5	0	Unknown 1 case not definitely established as laboratory infection	Unknown	Yes (1 case) Not tested (4 cases)	Not tested	Danhney et al. ¹¹⁷ Francis and Magill ¹¹² and Magill ¹¹⁴
	1	0	Contact with infected animals	Unknown	Yes	Yes	Smith-hurn ¹¹⁵
Colorado tick fever	1§§	0	Laboratory accident patient handled infected mouse brain	7	Not tested	Yes	Koprowski ^{119,118}
Mumps	1	0	Laboratory accident — contamination of mouth with infected monkey parotid gland	12	Not tested	Yes***	Enders et al. ¹²⁰
	1	0	Patient handled infectious saliva	Unknown	Yes	No	Levaditi et al. ¹²¹
	1	0	Sneezing of chimpanzee during attempt to inoculate intranasally with oral washings from patients	10-15	Yes	Not tested	Lepine ²⁴
Influenza	1	0	Laboratory accident — contamination of mouth by suction	1½	Yes	Yes	Dinger ¹⁰⁴
	4	0	Animals experimentally infected with virus	Unknown (2 cases) ≤2 (2 cases)	Yes (3 cases) Not tested (1 case)	Yes (2 cases) Not tested (2 cases)	Smith and Stuart-Harris ¹²² Laidlaw ¹²³ Sulkin ⁶⁴ and Francis ¹²⁵
	1	0	Patient worked with virus of chick-embryo origin	3	Not tested	Not tested	Lacortel ¹
	1	0	Patient worked with throat washings from infected patients not definitely established as laboratory infection	≤5 (?)	Not tested	Not tested	Krueger ¹²⁷
Vaccine virus	3	0	Patients handled large amounts of rabbit-adapted virus	Unknown	Not tested	Not tested	Beard ⁹⁹
Hepatitis (of viral origin?)	3	0	Unknown — probably exposure to contaminated serum not definitely established as laboratory infection	Unknown	Not tested	Not tested	Shanghnessy ¹²⁸ Hampill ¹²⁹ and Stokes ¹³⁰
	1	0	Not definitely established as laboratory infection, patient handled infected stools from infected patients	Unknown	Not tested	Not tested	Lepine ²⁴
German measles	1	0	Unknown — handling of throat washings and sputum from patient with German measles	≤14	Not tested	Not tested	Sigel ¹³¹
Viral diarrhea	1	0	Laboratory accident — contamination of mouth with corneal suspension	3	Yes	Yes	Dodd ¹³²

*Employed in the production of vaccine.

†Data not available regarding laboratory infections including fatal cases that occurred in Russia¹²‡One of these cases was reported by Critchley to Rivers and Schwentker¹⁰ in a personal communication.§Serum from one of these patients subsequently gave positive complement-fixation and neutralization tests with the Russian spring-summer encephalitis virus^{10,47}||Only 2 other human cases (both of which were fatal) have been recorded (Ohtaky and Casal¹⁶)¶One of these cases was reported by Plotz to Armstrong²¹ in a personal communication.**Antibodies still present nine years after infection (Milzer⁷⁹)

††The virus was also isolated by Dr. Minckness of the New York City Department of Health and by Dr. Armstrong of the National Institute of Health.

‡‡Neutralizing antibodies could be demonstrated in the serum of these patients four or five years after infection (Findlay¹⁰⁹)§§One of these cases was reported by Findlay to Kitchen¹¹²

|||Patient died from pulmonary embolism following thrombophlebitis after convalescence seemed assured.

¶¶This patient also had laboratory infections with the viruses of yellow fever¹⁰² and Rift Valley fever¹⁰⁷***Skin test was positive two months after onset of illness (Enders et al.¹²⁰)

TABLE 1 *Viral Infections Contracted in the Laboratory*

VIRUS	NO OF CASES	NO OF DEATHS	PROBABLE SOURCE OF INFECTION	INCUBATION PERIOD days	VIRUS RECOVERED	ANTIBODIES DEMONSTRATED	AUTHORS
Western equine encephalomyelitis (cases have occurred during animal experiments in Sweden ¹⁴ ; data concerning these experiments not yet available)	2*	1	Laboratory accidents: patients worked with virus of chick-embryo origin	14 (1 case) 4 (2 cases)	No (2 cases) Not tested (1 case)	Yes (2 cases) Not tested (1 case)	Helwig ¹⁵ Gold and Hamill ¹⁶ and Wright ¹⁷
	1*	1	Unknown patient worked with virus	<10	Yes	Not tested	Fothergill et al. ¹⁸
Eastern equine encephalomyelitis	1	0	Unknown patient worked with virus of chick-embryo origin	Unknown	Not tested	Yes	Olitsky and Morgan ¹¹
Venezuelan equine encephalomyelitis	4	0	Unknown patients worked with virus	Unknown	Yes (1 case) Not tested (2 cases)	Yes	Casals et al. ¹⁹ and Lennette ¹⁹
	8	0	Dust from contaminated mouse cages	3-11	Yes (6 cases)	Yes	Lennette and Koprowski ²⁰
	2	0	Unknown patients worked with virus of chick-embryo origin	3-4	Yes (1 case)	Yes	Koprowski and Cori ²¹
	2	0	Indirect contact, inhalation of infectious material; probable route of infection	3-4	Yes	Yes	Koprowski and Cori ²¹
Russian spring summer encephalitis†	1	0	Unknown patient worked with virus	Unknown	No	Yes	Olitsky ¹¹
Louping-ill	6‡	0	Unknown patients worked with virus	Unknown	Yes (1 case)	Yes	Rivers and Schwentker ²² Wichel ²³ and Weismeyer ²⁴
B virus ascending myelitis	1	1	Bite of apparently normal monkey	6	Yes	Not tested	Sabin and Wright ¹¹
Lymphocytic choriomeningitis (cases have occurred during animal experiments in Sweden; concern experiments available)	7*	0	Unknown patients worked with virus	Unknown	Yes (1 case) No (2 cases) Not tested (4 cases)	Yes (5 cases) No (1 case) Not tested (1 case)	Armstrong and Hornbrook, ²⁵ Armstrong, ²⁶ Dalldorf, ²⁷ Hammond ²⁸ and Salkin ²⁹
	3	0	Laboratory accidents during work with infected animal tissues	9 (1 case) 17 (1 case) 10 (1 case)	Yes (2 cases) Not tested (1 case)	Yes (3 cases)	Lepine and Senter ³⁰ Hayes and Hartman ³¹ and Milzer ³² 79
	2	0	One case not definitely established as laboratory infection; contact with mouse colony contaminated by virus previously described by Traub ³³ and closely related or immunologically identical with virus of acute lymphocytic choriomeningitis of Armstrong and Lillie ³⁴	Unknown	Yes	Yes	Rivers and Scott, ³⁵ 79 and Shope ³⁶
	1	0	Infected monkey lice	6	Yes	Yes**	Milzer and Levinson ³⁷
	1	0	Patient handled infected mice	Unknown	Not tested	Yes	Yamarat ³⁸
	1	1	No known contact with virus	Unknown	Yes	Not tested	Smadel et al. ³⁹ and Schroeder ⁴⁰
	1	1	Patient assisted at autopsy of fatal case reported by Smadel et al. ³⁹	8	Yes††	Not tested	Smadel et al. ³⁹ and Schroeder ⁴⁰
Durand's disease (virus D)	1	0	Unknown, not definitely established as laboratory infection	Unknown	Yes	Not tested	Durand ⁴¹
	1	0	Unknown patient worked with virus	4 (?)	Yes	Yes	Findlay ⁴²
Poliomyelitis	3	2	Contact with infected human or animal tissues	>9 (1 case) 21 (1 case) Unknown (1 case)	Yes (2 cases) No (1 case)	No (1 case) Not tested (2 cases)	Sabin and Ward, ⁴³ Wenner and Paul ⁴⁴ and Gear ⁴⁵
Mengo encephalomyelitis	1	0	Unknown patient worked with virus	5-8 (1)	Yes	Yes	Dick et al. ⁴⁶
Newcastle disease	2	0	Laboratory accidents during handling of infected allantoic fluid	1	Yes	Yes (1 case) No (1 case)	Bornet ⁴⁷ and Anderson ⁴⁸
	3	0	Patients worked with virus of chick-embryo origin	1 (1 case) Unknown (2 cases)	Not tested	Yes (1 case) Not tested (2 cases)	Beard, ⁴⁹ Shumkin ⁵⁰ and Howitt et al. ⁵¹
	1	0	Unknown	1	Yes	No	Anderson ⁴⁸
	5	0	Unknown, patients did not work with virus; possible aerogenic transmission	Unknown	Not tested	Yes	Howitt et al. ⁵¹
Yellow fever	21	2	Contact with infectious monkey blood or tissue	Unknown (18 cases) 10 (1) (2 cases) 3 (1 case)	Yes (16 cases) No (4 cases) No data (1 case)	Yes (7 cases) No (13 cases) No data (1 case)	Berry and Kitchen, ⁵² Low and Fairly, ⁵³ Longmann, ⁵⁴ Hindle, ⁵⁵ Snijders, ⁵⁶ Kuczynski, ⁵⁷ Kuczynski and Hohenadel, ⁵⁸ Burke and Davis, ⁵⁹ and Rockefeller Foundation ⁶⁰
	3	2	Bite of experimentally infected mosquitoes	Unknown	Yes (1 case) No (2 cases)	Yes (1 case) No (2 cases)	None, ⁶¹ Burke and Davis, ⁶² Rockefeller Foundation ⁶³

TABLE 1 (Continued)

VIRUS	NO OF CASES	NO OF DEATHS	PROBABLE SOURCE OF INFECTION	INCUBATION PERIOD	VIRUS RECOVERED	ANTIBODIES DEMONSTRATED	AUTHORS
				<i>days</i>			
Yellow fever	7	0	Handling of infected laboratory animals	Unknown (6 cases) 2 (1 case)	Yes (4 cases) No (3 cases)	Yes (6 cases) No (1 case)	Theiler ¹¹² Berry and Kitchen ¹¹³ Low and Fairly ¹¹⁴ Dinger ¹¹⁵ and Dinger et al ¹¹⁶
	2	1	Handling of infectious human blood	10	Yes (1 case) No (1 case)	Yes (1 case) Not tested (1 case)	Low and Fairly ¹¹⁴
	1	1	Autopsy on yellow fever patient	No data	Not tested	Not tested	None ¹¹⁸
	1	0	Unknown	Unknown	No	No	Rockefeller Foundation ¹¹⁷
Dengue fever	1	0	Contamination of conjunctival sac with human virus	10	No	Yes	Melnick et al ¹¹⁷ and Sabin ¹¹⁸
Rift Valley fever	3††	0	Patients performed autopsies on infected lambs	5-6	Yes (2 cases) No (1 case)	Yes	Findlay ¹¹⁹
	15‡‡	1	Unknown patients worked with virus	Unknown (12 cases) 6 (1 case) 4 (1 case) 7 (1 case)	Yes (14 cases) No (1 case)	Yes (12 cases) Not tested (3 cases)	Schwentker and Rivers ¹²¹ Kitchen ¹²² Francis and Magill ¹²³ Magill ¹²⁴ Sabin and Blumberg ¹²⁵ and Smithburn ¹²⁶
	5	0	Unknown 1 case not definitely established as laboratory infection	Unknown	Yes (1 case) Not tested (4 cases)	Not tested	Daubney et al, ¹²⁷ Francis and Magill ¹²³ and Magill ¹²⁴
	1	0	Contact with infected animals	Unknown	Yes	Yes	Smithburn ¹²⁸
	1†††	0	Laboratory accident—patient handled infected mouse brain	7	Not tested	Yes	Koprowski ^{129,130}
Colorado tick fever	1	0	Laboratory accident—contamination of mouth with infected monkey parotid gland	12	Not tested	Yes***	Enders et al, ¹³¹
Mumps	1	0	Patient handled infectious saliva ¹	Unknown	Yes	No	Levaditu et al ¹³²
	1	0	Sneezing of chimpanzee during attempt to inoculate intranasally with oral washings from patients	10-15	Yes	Not tested	Lepine ¹³⁴
	1	0	Laboratory accident—contamination of mouth by suction	1½	Yes	Yes	Dioger ¹³⁴
Influenza	4	0	Animals experimentally infected with virus	Unknown (2 cases) <2 (2 cases)	Yes (3 cases) Not tested (1 case)	Yes (2 cases) Not tested (2 cases)	Smith and Stuart-Harris ¹³⁵ Laidlaw ¹³⁶ Sulkin ¹³⁶ and Fraenkel ¹³⁶
	1	0	Patient worked with virus of chick-embryo origin	3	Not tested	Not tested	Lacorte ¹³⁸
	1	0	Patient worked with throat washings from infected patients not definitely established as laboratory infection	<5 (?)	Not tested	Not tested	Krueger ¹³⁷
Vaccine virus	3	0	Patients handled large amounts of rabbit-adapted virus	Unknown	Not tested	Not tested	Beard ¹³⁹
Hepatitis (of viral origin?)	3	0	Unknown—probably exposure to contaminated serum not definitely established as laboratory infection	Unknown	Not tested	Not tested	Shanghnessy ¹⁴⁰ Hampill ¹⁴¹ and Stokes ¹⁴²
	1	0	Not definitely established as laboratory infection, patient handled infected stools from infected patients	Unknown	Not tested	Not tested	Lepine ¹³⁴
German measles	1	0	Unknown—handling of throat washings and sputum from patient with German measles	<14	Not tested	Not tested	Sigel ¹⁴³
Viral diarrhea	1	0	Laboratory accident—contamination of mouth with corneal suspension	3	Yes	Yes	Dodd ¹⁴⁴

*Employed in the production of vaccine.

†Data not available regarding laboratory infections including fatal cases that occurred in Russia.¹³‡One of these cases was reported by Critchley to Rivers and Schwentker¹¹ in a personal communication.§Serum from one of these patients subsequently gave positive complement-fixation and neutralization tests with the Russian spring-summer encephalitis virus.^{18, 17}||Only 2 other human cases (both of which were fatal) have been recorded (Oltzky and Casals¹⁶)¶One of these cases was reported by Plotz to Armstrong²² in a personal communication**Antibodies still present nine years after infection (Milzer⁷⁹)

††The virus was also isolated by Dr Muckenfuss of the New York City Department of Health and by Dr Armstrong of the National Institute of Health.

‡‡Neutralizing antibodies could be demonstrated in the serum of these patients four or five years after infection (Findlay¹¹⁹)§§One of these cases was reported by Findlay to Kitchen.¹²²

|||Patient died from pulmonary embolism following thrombophlebitis after convalescence seemed assured

¶¶This patient also had laboratory infections with the viruses of yellow fever¹⁰ and Rift Valley fever¹¹²***Skin test was positive two months after onset of illness (Enders et al¹³¹)

TABLE 1 *Viral Infections Contracted in the Laboratory*

VIRUS	NO OF CASES	NO OF DEATHS	PROBABLE SOURCE OF INFECTION	INCUBATION PERIOD days	VIRUS RECOVERED	ANTIBODIES DEMONSTRATED	AUTHORS
Western equine encephalomyelitis (cases have occurred during animal experiments in Sweden ⁴⁴ data concerning these experiments not yet available)	2*	1	Laboratory accidents patients worked with virus of chick embryo origin	14 (1 case) 4 (2 cases)	No (2 cases) Not tested (1 case)	Yes (2 cases) Not tested (1 case)	Helwig ⁴⁴ Gold and Ham- pil ⁴⁴ and Wright ⁴⁷
	1*	1	Unknown patient worked with virus	<10	Yes	Not tested	Fothergill et al. ⁴⁴
Eastern equine encephalomyelitis	1	0	Unknown patient worked with virus of chick-embryo origin	Unknown	Not tested	Yes	Olitsky and Morgan ⁴⁴
Venezuelan equine encephalomyelitis	4	0	Unknown patients worked with virus	Unknown	Yes (1 case) Not tested (2 cases)	Yes	Casals et al. ⁴⁴ and Len- nette ⁴⁴
	8	0	Dist from contaminated mouse cages	3-11	Yes (6 cases)	Yes	Lenette and Koprow- ski ⁴⁴
	2	0	Unknown patients worked with virus of chick-embryo origin	3-4	Yes (1 case)	Yes	Koprowski and Cox ⁴⁴
	2	0	Indirect contact, inhalation of infectious material probable route of infection	3-4	Yes	Yes	Koprowski and Cox ⁴⁴
Russian spring-summer encephalitis†	1	0	Unknown patient worked with virus	Unknown	No	Yes	Olitsky ⁴⁴
Louping ill	6†	0	Unknown patients worked with virus	Unknown	Yes (1 case)	Yes	Rivers and Schwentker ⁴⁴ Wichel ⁴⁴ and Wexm- eler ⁴⁴
B viral ascending myelitis	1	1	Bite of apparently normal monkey	6	Yes	Not tested	Sabio and Wright ⁴⁴
Lymphocytic choriome- ningitis (cases have oc- curred during animal experiments in Swe- den ⁴⁴ data concern- ing these experiments not yet available)	7*	0	Unknown patients worked with virus	Unknown	Yes (1 case) No (2 cases) Not tested (4 cases)	Yes (5 cases) No (1 case) Not tested (1 case)	Armstrong and Horn- brook, ⁴⁴ Armstrong ⁴⁴ Dalldorf ⁴⁴ Hammon ⁴⁴ and Sulko ⁴⁴
	3	0	Laboratory accidents dur- ing work with infected animal tissues	9 (1 case) 17 (1 case) 10 (1 case)	Yes (2 cases) Not tested (1 case)	Yes (3 cases)	Lepine and Sautter ⁴⁴ Hayes and Hartman ⁴⁴ and Milzer ⁴⁴
	2	0	One case not definitely es- tablished as laboratory infection contact with mouse colony contam- inated by virus pre- viously described by Traub ⁴⁴ and closely re- lated or immunologically identical with virus of acute lymphocytic choriome- ningitis of Arm- strong and Lalbe. ⁴⁴	Unknown	Yes	Yes	Rivers and Scott, ⁴⁴ and Shope ⁴⁴
	1	0	Infected monkey lice	6	Yes	Yes**	Milzer and Levinson ⁴⁴
	1	0	Patient handled infected mice	Unknown	Not tested	Yes	Yamart ⁴⁴
	1	1	No known contact with virus	Unknown	Yes	Not tested	Smadel et al. ⁴⁴ and Schroeder ⁴⁴
	1	1	Patient assisted at autopsy of fatal case reported by Smadel et al. ⁴⁴	8	Yes††	Not tested	Smadel et al. ⁴⁴ and Schroeder ⁴⁴
Durand's disease (virus D)	1	0	Unknown, not definitely established as laboratory infection.	Unknown	Yes	Not tested	Durand ⁴⁴
	1	0	Unknown patient worked with virus	4 (?)	Yes	Yes	Findlay ⁴⁴
Poliomyelitis	3	2	Contact with infected hu- man or animal tissues	>9 (1 case) 21 (1 case) Unknown (1 case)	Yes (2 cases) No (1 case)	No (1 case) Not tested (2 cases)	Sabin and Ward, ⁴⁴ Wenner and Paul ⁴⁴ and Gear ⁴⁴
Measles encephalo- myelitis	1	0	Unknown patient worked with virus	5-8 (?)	Yes	Yes	Dick et al. ⁴⁴
Newcastle disease	2	0	Laboratory accidents dur- ing handling of infected allantoic fluid	1	Yes	Yes (1 case) No (1 case)	Bornet ⁴⁴ and Anderson ⁴⁴
	3	0	Patients worked with virus of chick-embryo origin	1 (1 case) Unknown (2 cases)	Not tested	Yes (1 case) Not tested (2 cases)	Beard, ⁴⁴ Shimkin ⁴⁴ and Howitt et al. ⁴⁴
	1	0	Unknown	1	Yes	No	Anderson ⁴⁴
	5	0	Unknown, patients did not work with virus possible aerogenic transmission.	Unknown	Not tested	Yes	Howitt et al. ⁴⁴
Yellow fever	21	2	Contact with infectious monkey blood or tissue	Unknown (18 cases) 10(?) (2 cases) 3 (1 case)	Yes (16 cases) No (4 cases) No data (1 case)	Yes (7 cases) No (13 cases) No data (1 case)	Berry and Kitchen ⁴⁴ Low and Farly ⁴⁴ Jung- mann, ⁴⁴ Hindle, ⁴⁴ H. Snijders ⁴⁴ Kuczyński ⁴⁴ Kuczyński and Hoben- adel, ⁴⁴ Burke and Davis, ⁴⁴ and Rocke- feller Foundation ⁴⁴
	3	2	Bite of experimentally in- fected mosquitoes	Unknown	Yes (1 case) No (2 cases)	Yes (1 case) No (2 cases)	None, ⁴⁴ Burke and Davis, ⁴⁴ Rockefeller Foundation ⁴⁴

TABLE C

VIRUS	NO OF CASES	NO OF DEATHS	PROBABLE SOURCE OF INFECTION	INCUBATION PERIOD	VIRUS RECOVERED	ANTIBODIES DEMONSTRATED	AUTHORS
Yellow fever	7	0	Handling of infected monkey carcasses	Unknown (11-12 days)	Yes (4 cases) No (3 cases)	Yes (6 cases) No (1 case)	Theiler ¹¹ , Berry and Kitchen ¹² , Low and Farley ¹³ , Dingle ¹⁴ and Dingle ¹⁵ et al. ¹⁶
	2	1	Handling of infected human blood	10	Yes (1 case) No (1 case)	Yes (1 case) Not tested (1 case)	Low and Farley ¹³
	1	1	An optical pyrexia patient	No case	No tested	Not tested	None ¹⁷
	1	0	Unknown	Unknown	No	No	Rockefeller Foundation ¹⁸
Dengue fever	1	0	Contaminated of blood of a patient with human virus	10	No	Yes	Wick ¹⁹ et al. ²⁰ and Sabin ²¹
Rubella fever	322	0	Patient's specimen of a specimen infected animal	5-6	Yes (2 cases) No (1 case)	Yes	Findlay ²²
	1544	1	Unknown patients with monkey virus	Unknown 6 (12 cases) 6 (1 case) 7 (1 case)	Yes (14 cases) No (1 case)	Yes (12 cases) No tested (3 cases)	Stewart ²³ and Rivers ²⁴ , Kitchen ²⁵ , Francis and Magill ²⁶ , Magill ²⁷ , Sabin ²⁸ and B. L. Sabin ²⁹ and S. L. Sabin ³⁰
	5	0	Unknown, known as definite, established as laboratory infection	Unknown	Yes (1 case) Not tested (4 cases)	Not tested	Dunbar ³¹ et al. ³² , Francis and Magill ³³ and Magill ³⁴
	1	0	Contact with infected animal	Unknown	Yes	Yes	Smith ³⁵
Colorado tick fever	155	0	Laboratory accident—patient handled infected monkey blood	7	Not tested	Yes	Reynolds ³⁶
Mumps	1	0	Laboratory accident—contamination of monkey with infected monkey parotid gland	12	Not tested	Yes ³⁷	Ender ³⁸ et al. ³⁹
	1	0	Patient handled infectious saliva	Unknown	Yes	No	Levinsky ⁴⁰ et al. ⁴¹
	1	0	Specimen of chimpanzee donated to hospital, subsequently found contaminated from patients	10-15	Yes	Not tested	Lepine ⁴²
Lassa	1	0	Laboratory accident—contamination of monkey by virus	172	Yes	Yes	Dingle ⁴³
	4	0	Animals experimentally infected with virus	Unknown (2 cases) <2 (2 cases)	Yes (3 cases) Not tested (1 case)	Yes (2 cases) Not tested (2 cases)	Smith and Stewart ⁴⁴ , Harris ⁴⁵ , Laidlaw ⁴⁶ , Sulkin ⁴⁷ and Francis ⁴⁸
	1	0	Patient worked with virus of chimpanzee origin	3	Not tested	Not tested	Lacoste ⁴⁹
	1	0	Patient worked with material from infected patients, not definitely established as laboratory infection	<5 (?)	Not tested	Not tested	Krukowski ⁵⁰
Vaccinia virus	3	0	Patient handled large amount of rabbit-adapted virus	Unknown	Not tested	Not tested	Beard ⁵¹
Hepatitis (of viral origin)	3	0	Unknown—probably exposure to contaminated serum, but definitely established as laboratory infection	Unknown	Not tested	Not tested	Shangraw ⁵² , Hamp ⁵³ and Slocum ⁵⁴
	1	0	Not definitely established as laboratory infection—patient handled infected serum from infected patients	Unknown	Not tested	Not tested	Lepine ⁴²
German measles	1	0	Unknown—handling of throat washings and sputum from patient with German measles	<14	Not tested	Not tested	Sigal ⁵⁵
Viral diarrhea	1	0	Laboratory accident—contamination of monkey with monkey suspension	3	Yes	Yes	Dodds ⁵⁶

*Employed in the production of vaccine.

†Data not available regarding laboratory infections, including fatal cases that occurred in Russia.⁵⁷‡One of these cases was reported by Crichtley to Rivers and Stewart⁵⁸ in a personal communication.§Sera from one of these patients subsequently gave positive complement-fixation and neutralization tests with the Panama spring-summer enterovirus.⁵⁹|| Only 2 other human cases (both of which were fatal) have been recorded (O'Leary and Carlini⁶⁰).¶One of these cases was reported by Plotz to Armstrong⁶¹ in a personal communication.**Antibodies still present one year after infection (Miller⁶²).

††The virus was also isolated by Dr. McCoskey of the New York City Department of Health, and by Dr. Armstrong of the National Institute of Health.

‡‡Neutralizing antibodies could be demonstrated in the serum of these patients four or five years after infection (Findlay²²).§§One of these cases was reported by Findlay to Kitchen⁶³.

||| Patient died from pneumonia following tracheostomy after convalescence seemed assured.

¶¶These patients had laboratory infections with the viruses of yellow fever⁶⁴ and Rubella fever⁶⁵ in***Sera from monkey after cases of Measles (Ender³⁸ et al.³⁹).

fever, psittacosis, Venezuelan equine encephalomyelitis and lymphocytic choriomeningitis. The laboratory infections with yellow-fever virus have previously been reviewed by Berry and Kitchen.⁹² It is of interest to note that, to our knowledge, no cases of laboratory-acquired yellow fever have occurred since introduction of vaccination. Also, it has been suggested that the use of the lyophilic process for drying of infectious material may have contributed to the eradication of this danger.¹⁵⁹ This provides an excellent illustration of the possible elimination of a hazard by improved technique.

experimental use of the virus.¹⁶² The 3 cases of vaccinia observed by Beard⁸⁹ occurred in persons handling large amounts of highly concentrated rabbit-adapted virus.

In several cases a virus disease was first recognized among laboratory personnel.* The 6 cases of infection with louping-ill virus were the only known human cases until 2 naturally acquired cases were reported in 1948.¹⁶⁴ The first infections with the Newcastle disease virus among human beings observed were laboratory infections involving the eyes.† Until the recent report by Howitt and her

TABLE 2 Laboratory Infections due to Agents of the Psittacosis-Lymphogranuloma-Venereum (*Chlamydozoaceae**) Group

VIRUS	NO OF CASES	NO OF DEATHS	PROBABLE SOURCE OF INFECTION	INCUBATION PERIOD days	VIRUS RECOVERED	ANTIBODIES DEMONSTRATED	AUTHOR
Psittacosis†	9	0	Laboratory accidents during work with virus	Unknown (3 cases) 7-14 (6 cases)	Yes (7 cases) No data (2 cases)	Yes (7 cases) No data (2 cases)	Rosebury et al. ¹⁵¹ and Meyer ¹⁵²
	16‡	2	Patients handled or autopsied infected or possibly infected birds	Unknown (3 cases) 14(?) (1 case) 10-14 (1 case) 7-10 (2 cases) No data (9 cases)	No data (11 cases) Yes (2 cases) Not tested (3 cases)	Yes (4 cases) No data (9 cases) Not tested (3 cases)	Meyer, ¹⁵³ Lepine, ¹⁵⁴ McCoy, ¹⁵⁵ and Moltke ¹⁵⁷
	14‡	0	Exposure to aerogenic transmission	Unknown (14 cases)	Yes (2 cases) No data (4 cases) Not tested (8 cases)	Yes (6 cases) Not tested (8 cases)	Meyer, ¹⁵³ Meyer and Eddies, ¹⁵⁶ and McCoy. ¹⁵⁵
	16§	5	Unknown patients worked with virus	6 (1 case) 8 (1 case) No data (3 cases) Unknown (10 cases) <15 (1 case)	Yes (4 cases) No data (11 cases) Not tested (1 case)	Yes (1 case) No data (12 cases) Not tested (3 cases)	Nonc, ¹⁵⁸ Rivers et al., ¹⁵⁹ Meyer, ¹⁵³ Cantu, ¹⁶⁰ Pfaffenberg, ¹⁶¹ Buchanan, ¹⁶² and Gilbert ¹⁶³
	11	0	Unknown	No data (11 cases)	Yes (1 case) No data (10 cases)	No data (11 cases)	Roubakine, ¹⁶⁴ Haagen and Kruckeberg, ¹⁶⁵ and Sturdee and Scott ¹⁶⁶
Lymphogranuloma venereum	3	0	Unknown patients worked with infected mice or chick-embryo and handled contaminated glassware.	Unknown	Not tested	Yes	Harrop et al., ¹⁶⁷ and Shaffer and Rakel ¹⁶⁸
	2	0	Unknown patients worked in laboratory where virus was studied	Unknown	Yes (1 case) No data (1 case)	Yes	Oliphant et al., ¹⁶⁹ and Shaffer and Rakel ¹⁶⁸
Atypical pneumonia	5	0	Unknown patients worked with virus	4-8 (1 case) Unknown (4 cases)	Yes (4 cases) Not tested (1 case)	Yes (3 cases) Not tested (2 cases)	Beck and Eaton, ¹⁷⁰ Meiklejohn et al., ¹⁷¹ Sven Gard, ¹⁷² and Bodily ¹⁷³

*Family name recommended by Breed et al.¹²³

†Numerous infections have occurred among dealers in birds.

‡The disease developed in 44 per cent of the personnel of a research laboratory in one building at the National Institute of Health.

§Rivers et al.¹⁵⁹ refer to infections that occurred in the laboratory of Dr. Krumwiede (New York City Department of Health) no details were given.

Recently, other workers¹⁶⁰⁻¹⁶¹ suggested improved procedures designed to remove the risk involved in the preparation of complement-fixing antigens.

The 24 cases of infection with Rift Valley fever virus point to the high infectivity of this virus, but none of the cases observed by Smithburn¹¹⁶ were severe. Death in the case reported by Schwentker and Rivers¹¹¹ occurred after recovery from the initial illness and was due to pulmonary embolism. Although many cases of ocular infection with vaccinia virus, usually associated with vaccination, have been reported, this infection rarely occurs as a laboratory accident in the course of preparation or

associates,⁹¹ the only naturally occurring human infections with this virus were also eye infections. The laboratory infections reported by these investigators were influenzal in nature, whereas the cases acquired outside the laboratory involved the central nervous system.

The original source of the "D" virus isolated by Durand⁸¹ in 1939 from his own blood during

*The first definite human infections with the virus of *Aujeszky's* disease (pseudorabies) were 2 cases of laboratory infection.¹⁶³ The virus was recovered from the blood in 1 case.

†Freymann and Bang¹⁶⁴ have reported 3 additional cases of conjunctivitis due to the virus of Newcastle disease in laboratory workers. The virus was isolated from 2 of these patients and antibodies were demonstrated in all 3.

a febrile illness is unknown. This agent, which was responsible for a single proved laboratory infection,⁵² has not been encountered in recent years.

The summary presented in the tables shows that the exact mode of infection in many cases is unknown, recognized accidents accounting for only 27 of the cases. The fatal case of encephalomyelitis reported by Helwig¹⁵ resulted when chick-embryo virus was thrown out of a centrifuge. The accidental splashing on the face of material from infected eggs was responsible for another case of encephalomyelitis¹⁶ and for 2 cases of infection with the virus of Newcastle disease.⁵⁷⁻⁵⁸ Three of the cases of lymphocytic choriomeningitis were associated with known accidents. In one,⁵⁷ a piece of glass flew into a worker's eye while infected guinea-pig organs were being ground in a mortar, in another⁵⁸ a celluloid tube containing the virus was flamed and in the third⁵⁹ the skin of the leg was accidentally punctured with a needle containing infectious material. The circumstances leading to a case of infection with psittacosis virus were carefully reconstructed by Rosebury and his associates¹³¹ to show how a leaking ampoule containing a suspension of volk-sac virus had contaminated the worker's hand and surrounding atmosphere. In the single case of B virus infection⁶¹ the worker was bitten on the finger by an apparently normal monkey. The bites of experimentally infected mosquitoes were thought to be responsible for 3 of the laboratory infections with yellow-fever virus.^{92, 100, 102} Contamination of the mouth by suction, a common laboratory accident, accounted for 1 case of influenza,¹⁰⁴ 1 case of mumps¹²¹ and 1 case of viral diarrhea.¹³² These instances illustrate the manner in which such accidents can occur, and suggest the nature of the precautions that should be taken by the laboratory worker handling infectious material.

The cases of infection among laboratory personnel apparently contracted during the handling of infected chick embryos attest to the potential infectiousness of such material. Chick-embryo virus was thought to be the source of infection in 2 cases of Western equine encephalomyelitis^{45, 46} in 4 cases of infection with Venezuelan equine encephalomyelitis virus⁵² and in the 1 case of Eastern equine encephalomyelitis.⁴⁹ Among the cases of psittacosis, of particular interest is a patient who had handled infected birds and mice for four years without infection but who became ill with proved psittacosis eight days after working with a suspension of virus from chick membranes.¹⁴⁰ The single case of meningopneumonitis-virus infection occurred in a person who had been using chick embryos for complement-fixation tests.¹³⁴ Seven cases of conjunctivitis due to Newcastle virus resulted from handling of infected chick-embryo fluids although Shumkin⁷⁰ referred to similar cases among kitchen workers handling food. Three cases of laboratory infection with the agent of lymphogranuloma venereum oc-

curred among persons working with infected chick embryos.¹⁴⁹ One factor that contributes to the danger in handling infected embryonated egg tissues may be the high concentration of virus in such material.¹⁶⁶

Several incidents show that a virus may retain its infectiousness for man even after many passages through animals. The strain of virus of Venezuelan equine encephalomyelitis responsible for the 8 infections reported by Lennette and Koprowski⁵¹ had been passed through mice about fifty times. The virus responsible for a case of Rift Valley fever had been through four hundred mouse passages¹¹² and another case at least three hundred mouse passages.¹¹⁵ The laboratory case of yellow fever reported by Theiler¹⁰³ was probably caused by mouse-adapted virus in the thirty-second passage. Influenza virus recovered from the person who contracted the disease from infected ferrets was pneumotropic when transferred back to the ferret.¹²² The alteration of the virus during animal passage, in this case, had not destroyed its infectiousness for man. Burnet and Bull¹⁴⁷ on the other hand found that passage of influenza virus through chick embryos rendered it noninfectious on intranasal instillation in man. Repeated passage of many viral agents in chick-embryo tissues may result in decreased virulence for the natural host.^{165, 169} In each of the 3 cases of poliomyelitis acquired in the laboratory the patient had been exposed to recently isolated strains.⁹⁻⁵⁵ During the two decades following the isolation of this virus the majority of work on experimental poliomyelitis was carried out with strains that were well established in the monkey in recent years, however, many investigators have attempted isolation of the virus from the patient. Coincidentally, the laboratory infection reported by Sabin and Ward³ in 1941 is the first recorded case of infection as a result of exposure to the virus in the laboratory. A second case of accidental infection with the virus was reported by Wenner and Paul⁵¹ in 1947, and more recently, we were advised of a third case by Gear.⁵⁵ In each case the patient had been exposed to strains of poliomyelitis virus recently isolated from human cases. For this reason workers in the field are cautioned to observe the greatest care in handling tissue or excreta of human subjects and in working with monkeys infected with this agent.

An analysis of the circumstances leading to certain of the laboratory infections has provided important information regarding the transmission of these diseases. Since contaminated dust from mouse cages was apparently responsible for the 8 infections with the virus of Venezuelan equine encephalomyelitis reported by Lennette and Koprowski,⁵¹ it seems likely that infection was by the respiratory route. Additional evidence for this possible route of infection is the fact that the virus was recovered from the nasopharyngeal washings

of 1 of the patients studied by Casals and his associates⁶⁰ and from 1 of the patients of Koprowski and Cox.⁶² The possibility of direct transmission of the equine-encephalomyelitis viruses suggested by these observations is of interest in connection with the evidence for insect and other ectoparasite vectors in these diseases.¹⁷⁰⁻¹⁷³

In addition to these cases of recognized illness, there have been an unknown number of inapparent infections as shown by the acquisition of antibodies by numerous laboratory workers. For example, Oltzky and Morgan⁴⁹ found protective antibodies for Eastern equine encephalomyelitis virus in the blood of 1 out of 6 laboratory workers who had handled the virus for several years. To account for this finding, they suggest the possibility of viremia without invasion of the central nervous system. Another case of antibodies for the same virus in a laboratory worker without recognized illness was recorded by Wright.⁴⁷ Beard⁸⁹ observed 2 inapparent infections with the virus of Eastern equine encephalomyelitis and 1 with the Western equine virus. Seven persons who had worked with the virus of Venezuelan equine encephalomyelitis, 1 who had bottled formalin-treated vaccine and 1 who had performed postmortem examinations on horses dying of encephalitis showed neutralizing antibodies for this virus. Only the last had an illness that was recognized as probable encephalitis. The serum from 6 persons residing in the same locality but who had no laboratory contact with the virus showed no mouse protection.¹⁷⁴ A number of subclinical infections with the Western equine encephalomyelitis virus evidenced by positive neutralization tests occurred among workers producing large amounts of vaccine of chick-embryo origin.¹⁷⁶ Neutralizing antibodies for the virus of St. Louis encephalitis have appeared in the blood of a person who worked with this virus intermittently for seven years.⁷⁰ In this laboratory the development of neutralizing antibodies for equine encephalomyelitis virus has been observed in a person who worked with the virus without clinical signs of infection.⁶⁶

A number of inapparent infections with the lymphocytic-choriomeningitis virus have been reported in animal caretakers.^{76 176 177} At a time when 2 fatal laboratory infections with the virus of lymphocytic choriomeningitis occurred, a number of inapparent infections were detected by serologic study among other members of the laboratory personnel.^{79 80} An inapparent infection with the virus of louping ill occurred at the same time as 3 apparent laboratory infections.^{84 85} One person working with the virus of Ilheus encephalitis developed a significantly high titer of neutralizing antibodies for this virus.^{118 178} An inapparent infection with mumps virus in a technician engaged in performing complement-fixation tests for mumps was reported by Enders and his associates,¹²¹ and another case was observed at the Pasteur Institute at the same

time that an overt infection occurred.⁸⁴ Two persons working with West Nile virus developed neutralizing antibodies without clinical symptoms.¹⁷⁹ A positive Frei test was recorded in a person a few months after he began working with the agent of lymphogranuloma venereum.¹⁸⁰ Four inapparent infections with the virus of Newcastle disease occurred at the time when 6 possible laboratory infections were observed.⁹¹ One investigator contracted an inapparent infection with the virus of Russian spring-summer encephalitis while working with the agent.¹⁸¹ In contrast to the above experiences, in some laboratories in which extensive virus work has been done no accidental viral infections have occurred, nor has there been evidence of inapparent infection.^{84 127 182-184} Although work with the rabies virus is done in many laboratories, to our knowledge there are no recorded cases of laboratory infections other than those acquired by persons carrying out post-mortem examinations on naturally infected animals.

SUMMARY

From published reports and from personal communications, 222 laboratory infections due to viruses are summarized. There were 21 deaths. The numerous viral agents involved include many that have been extensively studied, with the notable exception of rabies. Five viruses—namely those of psittacosis, yellow fever, Rift Valley fever, lymphocytic choriomeningitis and Venezuelan equine encephalomyelitis—accounted for over two thirds of the cases. An analysis of the probable source of these infections revealed that at least a third of the patients had become infected while handling infectious animals or tissues, 30 were presumed to have been exposed to a contaminated atmosphere, 13 had handled infectious material from patients, and 19 had worked with material from infected chick embryos. Known accidents were responsible for only 27 of the cases, these include a variety of situations, the most common involving the splashing of infectious material in the face or eyes. The first recognized cases of human infection with the viruses of louping ill and Newcastle disease were contracted in the laboratory. The data also reveal information regarding incubation periods and the route of infection in certain viral diseases.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 35311

PRESENTATION OF CASE

A thirty-seven-year-old machinist was admitted to the hospital because of sterility.

He had been married for a year and a half. His wife was thirty-nine years old and was said to be normal and fertile. One year before admission two examiners had reported no motile spermatozoa and elsewhere he had been treated with a high-protein diet, thyroid and vitamin E. A third doctor gave him chorionic gonadotropic hormone. He admitted exposure to venereal disease but denied its presence by signs and symptoms. Intercourse was normal. The family history revealed the mother to be living, the father had died of coronary-artery disease. One brother and a sister were married and had children. There was no family history of twins. The patient had a middle-ear infection at the age of one and again at eleven, a mastoidectomy at age seven, circumcision at age thirteen and appendectomy at age thirty-four. At the age of thirty-five he was admitted to the hospital for acute abdominal and back pain. At that time his studies were essentially negative except for narrowing of the joint spaces between the eleventh and twelfth dorsal vertebrae, which were fused, the abnormality being considered congenital. A gastrointestinal series was normal. Examination of the spine was negative. A retrograde pyelogram

was suggestive of stone at the lower end of the left ureter. A bladder culture was negative and the patient was discharged with the diagnosis of acute back strain. In the last two years he had felt logy, and the basal metabolic rate was said to be a "low normal."

Physical examination revealed a normal man of small stature who weighed 150 pounds and was 5 feet, 8 inches in height. The eyes, ears, nose and throat were normal, as were the heart and lungs. Examination of the abdomen was negative. The external genitalia were normal grossly on inspection and palpation. The prostate was normal in size and consistence. The examination of the prostatic secretion revealed no white cells.

The blood pressure was 120 systolic, 80 diastolic. The pulse was 80.

Examinations of the blood and urine were negative. A urine culture was negative. Two semen analyses revealed no spermatozoa. The follicle-stimulating-hormone qualitative test was negative and later positive for 6 mouse units for twenty-four hours. The 17 ketosteroids were 11.2 mg per twenty-four hours and later 10.7 mg.

An attempt was made to catheterize the ejaculatory ducts, and the operator's note was as follows:

The patient had a rather large flat verumontanum. Both ejaculatory ducts were visualized and catheterized for 1 cm. Good seminal vesiculograms could not be made because the dye exuded from the hole which was beyond the amount of catheter inside the ejaculatory duct.

A testicular biopsy was reported as "No diagnostic abnormality recognized." An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR FLETCHER H COLBY: This is obviously a case of male sterility with azoospermia. There are so many factors that come into male sterility that it is difficult to discuss them all. At least we can say that male fertility is a rather delicately balanced affair. It is easily affected by many things, such as the patient's general condition, disturbances of the endocrine glands and temperature changes. A good many years ago Dr Carl Moore, of Chicago, demonstrated the effect of heat on spermatogenesis. The temperature in the scrotum is believed to be lower than that in the inguinal canal or in the abdomen itself. He thought that this was why un-

descended testes have inadequate spermatogenesis Dr Moore's* studies were interesting and carefully controlled. He found that a fertile ram that had an oil silk bag tied over the scrotum soon lost active spermatogenesis. I saw an example of this a few years ago in a male sterility patient who had a small varicocele. In examining this patient I noticed that he wore a suspensory. I asked him how long he had worn it, and he replied three years, night and day. I suggested that instead of having the varicocele removed he take off the suspensory and send in another semen specimen. The first semen specimen showed 20,000,000 sperms per cubic centimeter. The next specimen, one month after the suspensory had been removed, showed 50,000,000, and he reported to me within the next month that his wife was pregnant.

The chief causes for azoospermia are occlusion of the seminal ducts from an inflammatory process, developmental defects, neoplasms of the genital tract and exposure to x-rays. Genital-tract infections as a cause of low fertility have never been adequately evaluated. We have all seen men who have a marked degree of infection in the prostate and seminal vesicle who have no difficulty in getting their wives pregnant. A recent patient with severe genital-tract tuberculosis, impregnated his wife in spite of the infection.

This patient gave no history of infection of the genital tract. The urine was sterile on culture, and the prostatic secretion was normal. Occlusion of the seminal ducts from inflammation, specific or nonspecific in character, was eliminated.

Neoplasms that may affect male fertility are new growths of the testes or spermatic cords or tumors within the prostatic urethra. There was no evidence of neoplasm in this patient. The presence of a papillary tumor of the prostatic urethra that could occlude the ejaculatory ducts may be dismissed by the attempt to catheterize the ejaculatory ducts. Failure to obtain seminal vesiculograms does not necessarily mean any abnormality of the ejaculatory ducts or seminal vesicles.

There is no history of exposure to x-rays.

Thus, we are brought to a defect in development as a cause for the azoospermia. Such a possibility is strengthened somewhat by the fact that a congenital defect of the vertebrae was demonstrated

by x-ray study, and where one congenital defect is present others are likely to exist. The congenital defects that may produce azoospermia are absence of the testes, imperfect testicular descent, imperfect spermatogenesis and congenital abnormalities of the epididymides and vasa deferentia. The testicular biopsy proved that both testes were normal, with active spermatogenesis. We are therefore left with the only remaining possibility—a congenital abnormality between the testes and the ejaculatory ducts. I should suppose the operation performed was to demonstrate this block in the seminal ducts, with the possibility, if conditions were favorable, of performing an epididymovasostomy.

This patient had been subjected to various forms of therapy in an attempt to improve his fertility, and illustrates the value of testicular biopsy in cases of azoospermia before treatment for male sterility is given.

DR ANNE P. FORBES: Would the testicular biopsy be normal with long-standing obstruction due to congenital atresia?

DR TRACY B. MALLORY: Can you answer that, Dr Sniffen?

DR RONALD SNIFFEN: Yes, the biopsy could be normal.

CLINICAL DIAGNOSIS

Congenital absence of vas deferens

DR COLBY'S DIAGNOSIS

Azoospermia due to congenital block in ducts

ANATOMICAL DIAGNOSES

Azoospermia

Congenital absence of vas deferens

PATHOLOGICAL DISCUSSION

DR FRED A. SIMMONS: May I read my operative note?

Under spinal anesthesia a 3.8 cm incision was made in the right scrotum, exposing the testis and epididymis. The testis was grossly normal. The epididymis was normal in the region of the globus major but rapidly thinned out into a fibrous band, and there was no evident globus minor or vas deferens. The spermatic cord was investigated thoroughly in various places, and there was nothing with any resemblance to a vas deferens. In this case fibrous substance appeared into nothing at all, and no trace of a vas deferens could be found. The epididymis was normal in size. A biopsy was taken from the right testis. The same procedure was carried out on the left side.

*Moore, C. R. Physiology of testis and application of male sex hormone. *J Urol* 47:51-44, 1942.

My interest in presenting this case is to bring to the attention of the group the fact that the treatment this patient had before testicular biopsy was unnecessary because he was a normal man with obvious reason for infertility. The simplest way to make a diagnosis of infertility when there is no history of inflammatory disease is to take a biopsy from the testis and examine it microscopically. The specimen need not be any larger than the head of a hatpin. One of these patients, a man of twenty-nine, had perfectly normal testes and living spermatozoa in the epididymides, although he had obstruction.

We had 5 cases with epididymitis on the basis of gonorrhea, all with living spermatozoa in the epididymis. All but 1 had testicular biopsies reported as normal. I do not believe that fact is generally known in the literature, and often patients are deprived of having children.

DR SNIFFEN: In all our cases (about 50) of congenital or acquired defects in the excretory ducts the testicular biopsy has shown active spermatogenesis. One other condition that one might mention in a discussion of azoospermia is the complete absence of germ cells in an otherwise histologically normal testis. The cause of this abnormality is not known. It is apt to be associated with an abnormally high output of pituitary gonadotropins—

CASE 35312

PRESENTATION OF CASE

A seventy-two-year-old Italian man was admitted to the hospital because of a lump over the left breast.

Two years previous to admission the patient noticed a small, freely movable mass, the size of a bean, developing over the left breast just to the right of the nipple. It caused no pain or discomfort but continued growing. The patient denied any loss of weight or appetite.

Physical examination revealed a tumor mass, 6 by 8 by 2.5 cm, located just to the right of the left nipple between the fourth and sixth interspace. It was firm over the lateral part, softer over the medial and cystic in the center. The surface was rather smooth except for a nodule felt over the lateral part. It was adherent to the skin but not to the underlying muscle. The nipple was very slightly retracted, but there were no changes on

the overlying skin. There were no enlarged axillary lymph nodes. Multiple warts were found over the back, and a small sebaceous cyst over the forehead. Examination of the lungs, heart and abdomen was negative.

The blood pressure was 155 systolic, 85 diastolic.

Urinalysis revealed no abnormalities. The hemoglobin was 11.5 gm per 100 cc, and the white-cell count was 9800.

The x-ray examination of the chest revealed fibrocalcific scars in the upper-lung fields. Both upper lobes were reduced in size, and there was a partially calcified, 2-cm lymph node at the right hilus. The left breast was enlarged and was particularly well shown in the lateral projection, in which view there was a suggestion of a small calcium fleck at the base.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR RICHARD H. WALLACE: May we see the x-ray films?

DR STANLEY M. WYMAN: The upper-lung fields show dense, fibrotic, partially calcified scars. The upper lobes are reduced in size, and the hili are elevated. There is a suggestion of a lymph node at the right hilus with some calcification within the node. The heart shadow is not remarkable. The aorta is probably calcified. The shadow of the left breast is well seen in the lateral view when viewed in a bright light and can be seen in the posteroanterior projection. The calcification described at its base probably represents calcified costal cartilage, rather than actual calcification in the tumor itself.

DR WALLACE: This is really a rare case when we consider how unusual tumors in the male breast are in general. If one rules out senile mastitis or, better named, senile masoplasia and the enlargement of the male breast that follows hormone therapy, it is really very rare.

Carcinoma of the male breast comprises only about 1 per cent of all breast cancer. In the last 680 cases that Dr Taylor and I reviewed from this hospital, there were only 4 cases of carcinoma of the male breast. However, this series included only cases with radical mastectomy. This particular case was certainly not the usual straight-

forward type of carcinoma — so it probably was something very unusual

It was a tumor of two years' duration, starting as a small, movable, bean-sized mass that increased to the size of 6 by 8 cm, which is a fairly good-sized tumor, as one can see by the x-ray film. One interesting thing is the variation in the consistence of the tumor. It was hard and nodular on one side and soft on the other, with a cystic center, but there is no mention of transillumination, which might have been helpful, especially in the presence of fluid. Transillumination might well have shown the presence of dark, rather than light, clear fluid, which would be helpful. The dark fluid might be blood or old blood or broken-down tumor, which, of course, would influence one a little on deciding whether or not the tumor was malignant.

There was adherence to the skin. I am assuming that this was not inflammatory because of its duration and behavior and the absence of signs of inflammation. A tumor that involves the skin with adherence is practically always malignant. One confusing exception to that is fat necrosis, which can cause the picture that we generally consider characteristic, clinically, of carcinoma of the breast. There was no history of trauma in this case, and I do not believe that a tumor 6 by 8 cm is very likely to have been — or, rather, I just do not believe that it could have been — fat necrosis. The nipple was slightly retracted, and, again, that suggests an invasive tumor. Of course, in the male the ductal portions are more likely to be involved than in the female. There were no palpable axillary nodes. That of course does not necessarily mean that this was benign. Some of the large tumors of the breast are found to be low-grade tumors and do not metastasize to the axilla. If it should be sarcoma, it is extremely rare to have sarcoma of the breast metastasize to the axilla.

It comes down to the question, Was this a malignant tumor or not? Perhaps there is some lead in this history, which to me might be misleading — that is, the sign of old tuberculosis within the chest. Whether or not this calcified fleck is in the tumor or not, as Dr Wyman has said, is not definite by x-ray study. Could this have been tuberculosis with a broken-down area? I think it is extremely unlikely. I am not doing any more than considering the possibility. We do occasionally see calcium in breast tumors, usually as a result

of long-standing tumor with hemorrhage either in the tumor or into a cystic area. It occurs occasionally in the long-standing papillary intraductal tumors that frequently bleed. Sometimes such a tumor will go on for a long time before it changes to become malignant, and old blood, either in the tumor from a small hemorrhage into the tumor or in the fluid, may cause calcification. Occasionally, a low-grade sarcoma of long standing will have areas of calcification. It certainly is an unusual tumor and, to my mind, it comes down to whether or not this was a carcinoma, probably arising in a papillary tumor, a fairly low-grade acinar tumor with degenerative areas or sarcoma of the breast.

DR IRA T NATHANSON. As Dr Wallace pointed out, this is a very unusual type of tumor of the male breast. We have recently reviewed the records of a large number of male patients with breast disease. The large majority of lesions are benign. The physical and histologic characteristics in older men are very much the same as those commonly observed in boys at puberty. In fact, these lesions in the male are akin to the early development of the breast in the female. Clinically, the lesions are represented by firm, well localized, movable and disk-like masses of varying size in the subareolar area. Tenderness is a common feature. There is no evidence of skin attachment or invasion or retraction of the nipple. Histologic appearance is one of an increase and branching of the rudimentary duct systems, with accompanying fibrosis. Alveolar development is rare. The location of these lesions can be easily explained by the fact that the anlage of the breast is immediately beneath the nipple. These lesions in the male may be entirely unilateral or involve both breasts simultaneously or successively. The lesions in contrast to those arising as a result of disease elsewhere,* are considered an integral part of hormonal alterations occurring during puberty or at the climacteric. As a rule these lesions regress spontaneously in both the young and the older males. Diagnosis is usually made without difficulty by those cognizant with the syndrome, and the patients are usually treated conservatively although careful observation is advised. If there is no regression after a reasonable period, excision is advised primarily for psychologic and

*Nathanson I T. Relationship of hormones to diseases of breast. *Surg 16* 108-140 1944

cosmetic reasons in the pubertal male. Cancer must be excluded by exploration in the older male if the process persists even in the absence of definite signs.

A study of almost 100 cases of proved cancer of the breast in the male has revealed that the diagnosis was made with few exceptions at the first examination. These tumors usually arise also in the subareolar area. But, in this case, there is evidence of invasion as manifested by dimpling or adherence to the skin, fixation to deeper structures and retraction of the nipple. This may occur early in the course of the disease since there is less breast tissue and usually less subcutaneous fat in the male. This characteristic may also permit easier accessibility of the tumor to routes of metastases.

Consequently, one would believe, as Dr. Wallace does, that the lesion under discussion was a malignant process because it presented two suggestive earmarks of cancer: skin adherence and retraction of the nipple. The prognosis of cancer in the male breast is less favorable than that in the female. This is probably due to the usually more advanced stage of the disease when the patient is first seen. Tenderness, a common feature of a benign process, is usually absent, and as a result the patient is frequently unconcerned until the diagnostic features of cancer are obvious. To reiterate, the lesion in this patient is rare, for most of the cancers in the male breast are of the more malignant type and invade and ulcerate early.

CLINICAL DIAGNOSIS

Carcinoma of breast?

DR. WALLACE'S DIAGNOSIS

Carcinoma arising in intraductal papilloma

ANATOMICAL DIAGNOSIS

Papillary adenocarcinoma of breast

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The specimen we received showed a partially solid, partially cystic tumor, which evidently had originally been an intraductal adenoma but had become slightly invasive at the periphery and was classified as a papillary adenocarcinoma of low-grade malignancy. It contained a great many flecks of calcium scattered throughout the tumor: small, round, concentric spheres, looking very much like corpora amylacea or the psammoma bodies that one sees in ovarian tumors. That is a distinctly unusual feature, and I do not offhand recall another breast tumor showing it. I believe, in view of various factors in the patient's condition, it was thought not wise to do a radical operation in this case, and a simple mastectomy was done.

DR. NATHANSON: The patient was discussed in the tumor clinic conference. A simple mastectomy was advised because it was thought to be a benign process. Once the final diagnosis became obvious, it was the consensus of the clinic, in conjunction with Dr. Castleman's opinion, that the patient would get by with a simple mastectomy. We would have done a radical resection had we suspected the diagnosis before operation. Do you agree, Dr. Taylor?

DR. GRANTLEY W. TAYLOR: Yes.

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THE EPIDEMIOLOGY OF MORALS

TIME was when the public-health officer was verbally if not actually stoned for tacking the red scarlet-fever sign on the door — when the legal diagnosis of contagious disease and enforced quarantine was an un-American invasion of the family's and the family doctor's rights. The country has come a long way. Recently the United States Public Health Service has entered new and wider areas of investigation for instance, community surveys of heart disease and diabetes, and latterly the incidence of marriage and divorce.

All pollsters are to be feared, even those bearing such fascinating gifts as Dr. Kinsey and his colleagues do. One cannot yet picture the hurried census taker or the eager district health worker inquiring after the waxing and waning of the nest-

ing instinct in a harassed housewife at 10 o'clock in the morning. Nevertheless the interest of public-health authorities in the plain, uninterpreted figures on marriage and divorce means a beginning in the epidemiology of morals.

The Federal Security Agency's Public Health Service announces that both marriages and divorces have declined in the last two years, there being one third fewer divorces in 1948 than in the peak year 1946, when 610,000 divorces were granted. In 1948 there were one eighth fewer divorces than in 1947. The decline in divorce rate per 1000 in the three years is 4.3, 3.3 and 2.8. In 1946 there were 2,000,000 marriages, and in 1948 about 500,000 less. Marriage rates per 1000 in these three years were 16.4, 13.9 and 12.4.

There is no cause for encouragement in these figures on the brief postwar span. The heightened sense of so little time during the war doubtless intensified the urge to procreate, the appetite for the fullness of life experience or the search for emotional security in marriage. The special war situation in this respect has passed, and there are those who estimate that one in three marriages may still end in divorce. When statistics are reviewed over several decades,¹ it is found that both marriage and divorce have increased in relative frequency. The figures, moreover, do not indicate the effects of disrupted marriage on the children, the parents or society as a whole.

Most very young women are clear about the future. They plan to marry. As a young lady recently said to her father who was chiding her about a poor school report: "You don't need a diploma to get married." Most young men, it should be admitted, do not know what it is all about when they get married. The question, if not actually popped by the girl, is by pressures or contrivances put in the young man's mouth. In short, if he knows what he is doing, the young man is not in love. Marriages for sex alone soon pall and quickly fall apart. Marriages for children alone, after some years, find the mother without a job when her offspring are grown and in college or off on careers or marriages of their own, while the middle-aged father, aware of his failing powers, looks for a corn-haired sweetie to restore his confidence. How many friends for

whom one stood at the altar twenty-five years ago ask advice now because of a vague sense of cracking up and the windy melancholy, suggesting that one prescribe or approve a change of job, of locality and especially of wife! This was one of the factors that made the forty-five-year-olds so belligerent during the recent war. Contrariwise, not a few of the women approaching middle age, their tubes tied or the uterus removed on some pretext or other, have a sexual eagerness not easily satisfied by their disenchanting husbands. With all its rationalizations, divorce often is really a very banal affair of the glands and other monkey business. Divorce may be cunning or slick or smart, but it is not often intelligent. It is impulsive or instinctive, it may even result from an honest affair of the heart, but not of the educated or understanding heart.

Sigmund Freud² states that the id and the super ego struggle for the ego, which makes an uncertain compromise called neurosis or civilization. On this naturalistic basis there is reason for marriage in that it conserves the libido, the work of the world and human creativeness in this view are mere sublimations. In the gospel according to St Paul, nineteen centuries ago, neurosis was well described and in closely similar terms. "For the flesh lusteth against the spirit and the spirit against the flesh and these are contrary the one to the other so that ye cannot do the things ye would" (*Galatians* 5:17). The basis of this gospel is not naturalistic but is one of values not susceptible to proof by reason alone. The resolution of the neurosis is not by a life-long haggling in the economics of pleasure and pain but by the growing realization of individuality in devotion to another's good. The physiology of these opposite assumptions is identical. The one remains natural, the other adds that which makes man different from animals—the capacity to retain values and to pass them from generation to generation.

In this realm of values, human relations at their hoped-for best, and indeed man's relation to his universe, are represented in terms of family ties. An epidemiology of morals is a welcome barometer for the spiritual climate, apprising one of fair or foul weather ahead. At the moment the glass seems to be still falling in spite of the cheery figures from

the Surgeon General. In these seas the general practitioner is more weathervise. He should consult his own traditions and his best insights and appropriately admonish the voyagers committed to his care.

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BRITISH-AMERICAN EXCHANGE FELLOWSHIPS IN CANCER RESEARCH

OF GREAT interest is the recent announcement that the American Cancer Society, in conjunction with the British Empire Cancer Campaign, is offering British-American exchange fellowships in cancer research. The fellowships will provide specialized training for American investigators to study in Great Britain, where there are opportunities for study and research that are not generally available in this country. An equal number of young British scientists will be selected for specialized training in the United States.

The stipends are generous, and the fields of study offered suggest a sound approach to the problem of cancer in human beings. The annual stipend will be £1000 (\$4020), with an allowance of \$600 for travel to the site of the fellowship. The Committee on Growth of the National Research Council and the Empire Cancer Campaign must approve the institution where the applicant chooses to work and the persons under whose guidance he wishes to conduct his research, which should be applicable to problems of neoplastic growth in specialized scientific fields in which there are superior facilities in Great Britain.

The fellowships are open to United States citizens who possess the degree of doctor of medicine, doctor of philosophy or doctor of science, and are intended for young men and women entering a career in clinical medicine or basic research, as well as for more mature candidates who wish to extend their competence in these fields. Applicants must be able to show that they have the qualifications necessary to investigation in the fundamental sciences or in clinical medicine. Applications should contain reference to the institution in which the

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ing instinct in a harassed housewife at 10 o'clock in the morning. Nevertheless the interest of public-health authorities in the plain, uninterpreted figures on marriage and divorce means a beginning in the epidemiology of morals.

The Federal Security Agency's Public Health Service announces that both marriages and divorces have declined in the last two years, there being one third fewer divorces in 1948 than in the peak year 1946, when 610,000 divorces were granted. In 1948 there were one eighth fewer divorces than in 1947. The decline in divorce rate per 1000 in the three years is 4.3, 3.3 and 2.8. In 1946 there were 2,000,000 marriages, and in 1948 about 500,000 less. Marriage rates per 1000 in these three years were 16.4, 13.9 and 12.4.

There is no cause for encouragement in these figures on the brief postwar span. The heightened sense of so little time during the war doubtless intensified the urge to procreate, the appetite for the fullness of life experience or the search for emotional security in marriage. The special war situation in this respect has passed, and there are those who estimate that one in three marriages may still end in divorce. When statistics are reviewed over several decades,¹ it is found that both marriage and divorce have increased in relative frequency. The figures, moreover, do not indicate the effects of disrupted marriage on the children, the parents or society as a whole.

Most very young women are clear about the future. They plan to marry. As a young lady recently said to her father who was chiding her about a poor school report: "You don't need a diploma to get married." Most young men, it should be admitted, do not know what it is all about when they get married. The question, if not actually popped by the girl, is by pressures or contrivances put in the young man's mouth. In short, if he knows what he is doing, the young man is not in love. Marriages for sex alone soon pall and quickly fall apart. Marriages for children alone, after some years, find the mother without a job when her offspring are grown and in college or off on careers or marriages of their own, while the middle-aged father, aware of his failing powers, looks for a corn-haired sweetie to restore his confidence. How many friends for

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COMPLETE ACROMIOCLAVICULAR DISLOCATION

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FOR a lesion that appears to be so simple, complete acromioclavicular dislocation can be one of the least satisfactory of traumatic injuries to treat. It is rarely difficult to reduce the dislocation but to *hold* the reduction is another matter.

STRUCTURE AND FUNCTION

This problem is best approached by a brief consideration of the structure and function of the parts involved. In man, the upper extremity is not normally used for weight bearing but largely for prehension and tactile information — uses that require an extreme degree of freedom and as full a range of motion as possible. Such mobility is assured through an anatomic strut, the clavicle, which holds the scapula well out from the central body axis, acting somewhat as the boom of a derrick.¹ At the outer end of this strut the scapula, a relatively large and heavy bone from which the whole upper extremity depends, joins the clavicle through a single small and inherently weak articulation. The average acromioclavicular-joint surfaces measure only 1.9 by 0.9 cm., the capsular ligaments are thin, and the joint is at an added mechanical disadvantage in that, in most cases, the articular surface of the acromion slightly underlies that of the clavicle.

Obviously re-enforcement is needed. It is provided by the dense, strong fibers of the coracoclavicular ligament, which occupy the 1.3-cm. space between the upper surface of the coracoid and the undersurface of the clavicle (Fig. 1). This ligament has no anatomic connection with the acromioclavicular joint, but it is essential to the proper functioning of that joint.¹⁻⁴ It is tough, but elastic and so arranged as to allow a small amount of motion in *all* axes at the joint, it should be noted that this includes some degree of rotation about the long axis of the clavicle.^{1, 5, 6} However, as Codman¹ has emphasized, "All these motions are very slight in degree and the range of the acromioclavicular joint is only the range of the pliability of the coracoclavicular ligaments themselves." Rarely,

the ligament is replaced by a joint,^{7, 9} but this is of academic rather than practical interest.

PATHOLOGY

In essence, the coracoclavicular ligament serves as a short, stout cord by which the scapula hangs from the outer end of the clavicle. If that cord is disrupted (Fig. 2) the acromioclavicular joint will dislocate, the outer end of the clavicle will move up and back, the scapula, with the upper extremity, will drop downward, forward and inward, and the patient will be unable to abduct his arm. This is the picture of complete acromioclavicular dislocation, and it is imperative, when repair is contemplated, that attention be focused not on the dislocated acromioclavicular joint but on the torn coracoclavicular ligament.

Healing takes place here, as elsewhere in the body, by scar formation. If the torn ends of the ligament are maintained in apposition during the six to eight weeks that healing requires, firm re-establishment of ligamentous integrity is the rule. An interesting observation is the frequency with which calcification, and later ossification, occurs within and about the torn ligament.¹⁰⁻¹² Whether this is due to hemorrhage or detachment of periosteum, or both, is a matter of conjecture. Apparently, it is an interesting pathological finding that is unrelated to the type of treatment used and, fortunately, has no adverse effect upon function or cosmesis.¹¹⁻¹³

Partial dislocation of the joint occurs when the capsular ligaments give way with little or no tearing of the coracoclavicular ligament, displacement is usually negligible, and the prognosis, with temporary external support, excellent. However, *complete* dislocation, which involves tearing of the coracoclavicular ligament, is the sole consideration here.

ETIOLOGY

Complete dislocation results from a severe blow impinging upon the acromion in such a way as violently and suddenly to depress it in its relation to the outer end of the clavicle. This occurs in one

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proposed study is to be conducted, the person under whom the candidate desires to work, the problem to be investigated and the date on which he wishes to begin his research. Appointment to the staff of a university, with teaching duties, is permitted, provided it carries no additional salary and is acceptable to the two organizations sponsoring the fellowships, as well as to the Committee on Growth. Once accepted, the fellowship may not be vacated, nor the place of work changed within the period of tenure without the consent of all three organizations.

Applications may be submitted at any time to the Executive Secretary of the Committee on Growth, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D C.

The fellowships should result in constructive progress in cancer research. It is to be expected that the applicants who benefit from the opportunity offered will also act as ambassadors of good will in the countries of their study.

WELFARE STATE

CONGRESS passed in June a record annual budget for public-health service that provided increases for mental health, cancer and heart research and aid to the various states. In addition a bill was introduced in the House, to which the medical profession certainly will not object, to raise the pay of all physicians, dentists and nurses in the Veterans Administration.

According to the terms of the Federal Security Agency's appropriations bill, 40 medical and 16 dental schools will receive \$872,477 for training in cancer, 31 institutions, including the American Cancer Society and the American College of Surgeons will share \$550,802 in special cancer-control-project grants, and 99 cancer-research projects will receive a total of \$1,026,294.

Congress has further voted \$100,000 for blue prints and specifications for the National Dental Research Institute to be built in Bethesda. (The American Dental Association favored \$2,000,000 to start immediate construction.)

According to the details published in *Washington Report on the Medical Sciences* for June 27,

National Heart Institute received a sizable \$10,725,000 plus contractual authority of \$5,350,000 for research and training grants. To National Cancer Institute went the record sum of \$18,900,000 and, in addition, \$6,000,000 in contractual authority. Another record figure of \$11,612,000 was voted for mental health. And still another, \$12,075,000 to National Institutes of Health, a large part of which will go for research, training, control and fellowship grants in noncategorized fields. Venereal disease activities get \$16,000,000, for general assistance to the states, \$16,600,000 is provided, communicable disease control functions receive \$7,350,000, \$167,000 is allocated for administering the Federal employe health program. For administration of the Hill-Burton hospital program, \$1,200,000 was approved, obviating a drastic reduction in force which would have resulted if the Senate had yielded to the House figure of \$1,000,000.

Without the aid of an adding machine the figures mentioned seem to total \$108,528,573. For no particular reason at all, snatches of a conversation at the Mad Hatter's tea party come to mind.

"And so these three little sisters" — (said the Dormouse) "— they were learning to draw, you know —"

"What did they draw?" said Alice.

"Treacle,*" said the Dormouse.

"But I don't understand" (said Alice), "Where did they draw the treacle from?"

"You can draw water out of a water well," said the Hatter, "so I should think you could draw treacle out of a treacle-well — eh, stupid?"

*Molasses

A physician has opened his office on board an Ohio steamboat. A mesmeric institution has been organized in the ancient city of Bristol, Eng., of which Earl Ducie is president. He is a decided believer in all kinds of moonshine.
Boston M & S J, August 1, 1849

MASSACHUSETTS MEDICAL SOCIETY



DEATH

KING — Francis B. King, M.D., of Derry, New Hampshire, died on July 10. He was in his forty-sixth year. Dr. King received his degree from Tufts College Medical School in 1934. He was formerly a member of the staffs of Boston City and Boston Psychopathic hospitals and Harper Hospital, Detroit. His widow, a daughter, a son, his mother and a brother survive.

(Notices on page xv)

clavicular dislocation excision of the outer end of the clavicle, fusion of the joint, and restoration of the joint

Excision of the Outer Portion of the Clavicle

In the past few years this has been strongly urged by the late Fraser Gurd¹⁰ for fresh injuries, by Mumford¹⁸ for persistent pain and disability from chronic lesions, and by Urist³⁵ for both. It is not a recent innovation. Removal of a greater or lesser part of the distal clavicle, for this and other lesions, has been practiced for years with acceptable results. Gurd² reported 2 successful cases, Urist³⁵ 9 and Mumford¹⁸ 4, but none of Mumford's patients had complete dislocation. In fact he recommended fascial suture in preference to clavicular excision for this lesion.

Fusion of the Acromioclavicular Joint

In 1943 Caldwell⁴¹ reported 2 cases of chronic complete acromioclavicular dislocation treated by fusion of the acromioclavicular joint with good results at twelve months and five months, respectively. In both patients abduction was limited. No other author has recommended this method in the last ten years.

Restoration of the Acromioclavicular Joint

Restoration of the acromioclavicular joint to its normal anatomic and functional status should constitute the best treatment if it can be accomplished without serious harm or disadvantage to the patient. The difficulty of bringing this about satisfactorily, however, is amply attested by the introduction of the radical procedures just considered as well as by the great variety of reparative techniques described in the literature, all of which fall into one or another of four fundamental groups: skeletal traction, syndesmopexy and ligamentoplasty, wire transfixion-fixation, and screw suspension.

Skeletal traction has few advocates. It may be applied in any one of several ways, but they all involve the very real danger of infection imposed by foreign bodies transfixing the skin for any length of time. This seems sufficient reason to condemn the method, especially since traction can be applied effectively without operation.^{38, 39}

*Syndesmopexy*⁴² and *ligamentoplasty*^{3, 18, 43, 51} may be considered together since they both aim at reapproximation of clavicle and coracoid process by suture material. In the former, foreign substances such as silk, wire and catgut are used, and in the latter autogenous fascia is employed.

Ligamentoplasty, certainly until recent years, has been the method most widely used in the treatment of complete acromioclavicular dislocations. It is subject to numerous modifications. A free graft of fascia lata or the coraco-acromial ligament⁴⁴ or a portion of the short head of the biceps brachii⁴⁵ may be used. These materials may be passed

completely around the clavicle and coracoid or through drill holes in the bones. Reinforcement is usually provided with silk, cotton, catgut or wire sutures. In 1 case a coracoclavicular screw was used to reinforce a repair made with part of the short head of the biceps.⁵²

Twelve good results with this repair have been reported by five different surgeons^{43-46, 48} in the last decade. Serious complications, such as infection and sloughing of the fascia, are not mentioned. However, it is known that they sometimes occur.⁵³ Some surgeons supplement the operative repair with a cast for four to six weeks.^{43, 44}

Wire transfixion-fixation was introduced by Gordon Murray¹³ in 1940 with the report of 5 cases successfully treated with Kirschner wires inserted horizontally through the acromion, across the joint and into the clavicle.

Phemister⁵⁴ prefers heavy threaded wires, which are removed after two months. He immobilizes the arm and forearm for one month and the arm alone for an additional month in a Velpeau bandage. He does not permit shoulder motion while the wires are in place for fear of their breaking. He reports 2 cases with excellent results at four years and five months, respectively.

Bloom⁵⁵ used wire transfixion-fixation in 12 cases in the Navy, with results that were presumed to be good because the men were rated as on active duty three and a half to ten months after the wires were removed.

Screw suspension^{6, 11, 56-59} is, as its name implies, a method of *suspending* the scapula from the clavicle by a vitallium lag screw (Fig. 3) until the torn coracoclavicular ligaments heal. It is *not* fixation.⁶⁰ This procedure accomplishes the effects of syndesmopexy and ligamentoplasty by a relatively simple and minor operation performed through a small incision under local anesthesia.

Certain points in technic are essential to success. The acromioclavicular joint must first be reduced. The hole in the clavicle should be somewhat larger than the screw shaft. The screw must be made to bite its own way into the coracoid, without previous drilling, and it should be set deeply enough firmly to grip both the upper and the lower cortices of the coracoid. Postoperative management includes immediate use of the extremity for all light activities, such as shaving and dressing. All lifting, pulling or pushing must be absolutely prohibited for eight weeks, since during this period the screw alone is depended upon for support.

In 1941 the first 4 cases in which this procedure was carried out were reported.⁶ Later, the method was independently devised by Vere-Hodge⁵⁸ in England, where it was used during the recent war. He has done 7 cases with very satisfactory results at three weeks to four years after operation.¹² Dyer⁵⁶ has reported 4 cases with excellent results at two to six months. Stewart⁵⁷ discussed 9 patients op-

of two ways either an object falls on the acromion or, more commonly, the patient falls and lands on the acromion

DIAGNOSIS

The distinction between partial and complete dislocation is an important one to make, since it affects treatment. The diagnosis of complete disruption is obvious in cases in which the tip of the clavicle lies free and high in the subcutaneous tis-

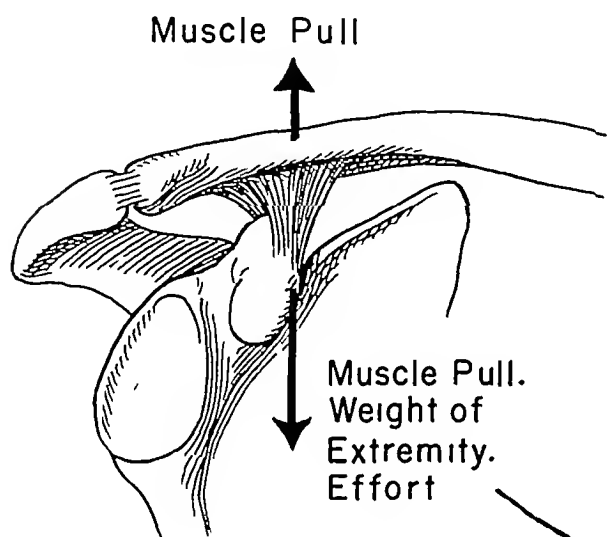


FIGURE 1 The Coracoclavicular Ligament, a Short, Stout Cord by Which the Scapula Hangs from the Outer End of the Clavicle

sue, tenting and nearly perforating the overlying skin. In other cases the diagnosis may be difficult. The best criterion is roentgenographic evidence of a widening of the space between the coracoid process and the overlying clavicle on the affected side, as compared with the other, normal, shoulder³ (Fig 2). This may easily be demonstrated on a single roentgenogram, taken to include both shoulders, with the patient standing. I have not found it necessary to have the patient hold a heavy weight in each hand,¹⁰ although this might be of assistance in some cases.

TREATMENT

Forms of treatment suggested for complete acromioclavicular dislocation fall into two main groups, operative and nonoperative.

NONOPERATIVE

This is an attempt to maintain reduction by externally applied pressure, or by traction, until healing of the torn coracoclavicular ligament has taken place. A review of the literature of the past decade reveals many methods aimed at accomplishing this result.

The procedures advocated include the following: adhesive (or other) strapping,¹⁴⁻²² a figure-of-8 bandage, as for fractured clavicle,²³ sling and pressure dressing,²⁴⁻²⁵ a "suspension hammock" with a cradle under the axilla,²⁶ a brachioclavicular splint,²⁷⁻²⁹ a thoracobrachial cast with pressure pad,³⁰⁻³⁶ a thoracic cast with axillary crutch³⁷ and abduction traction and suspension in bed.³⁸⁻³⁹

It is extremely difficult to compare results of these different methods for two reasons: careful studies of long-term end results are regrettably scarce, and many authors do not distinguish clearly between partial and complete dislocations.

Urist³⁵ recently presented a four-week follow-up study of 15 complete dislocations in young soldiers treated with the thoracobrachial cast and pressure pad. All were kept in the cast for six weeks and then

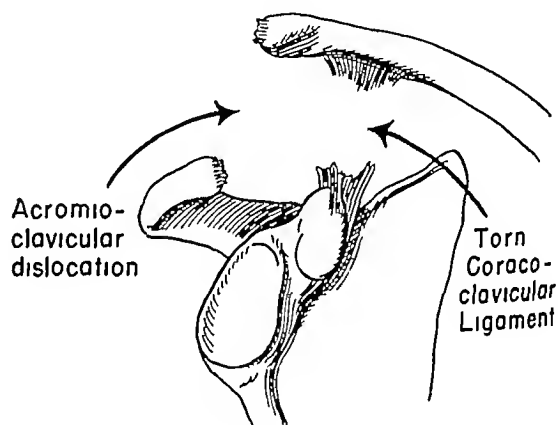


FIGURE 2 Rupture of the Coracoclavicular Ligament, Resulting in Complete Acromioclavicular Dislocation

had 2 weeks of physiotherapy. Among the 15 patients, there were 3 redislocations within four weeks, and in 2 of these cases symptoms were severe enough to require subsequent operative intervention. Thus, failure of conservative treatment was appreciable in a small but well controlled series of freshly incurred injuries in young healthy persons—all treated with the same nonoperative method by the same doctor. In an earlier paper Ehler⁴ reported excellent one-year to three-year results in 22 of 26 complete dislocations treated with a sling and pressure dressing. Howard²⁷ observed success in 8 out of 10 complete luxations treated with a brachioclavicular cast. Significant reports of end results obtained by the other conservative methods of treating complete acromioclavicular dislocations are lacking.

OPERATIVE TREATMENT

Three basically different surgical concepts have been followed in the treatment of complete acromio-

simpler operation is to be preferred, if its results are comparable to those of the more radical procedures

There are certain disadvantages inherent in wire transfixion-fixation. The acromioclavicular joint is completely immobilized, with consequent limitation of motion, for eight weeks. Two operations are required, for the wires must be removed. Wires that have migrated from the shoulder have had to be removed from the neck and even from the lung.⁶¹

The method of screw suspension is free of these objections. Mobilization of the upper extremity is assured from the day of operation. In fact, most patients feel so well that it is difficult to keep them from overdoing. In only the exceptional case need the screw ever be removed. I know of no case in which a screw has migrated to another part of the body. The operation is physiologically sound, suspensive reinforcement is provided at the exact point where it is required anatomically and functionally—and without fixation. No important structures are endangered by the screw.

SUMMARY

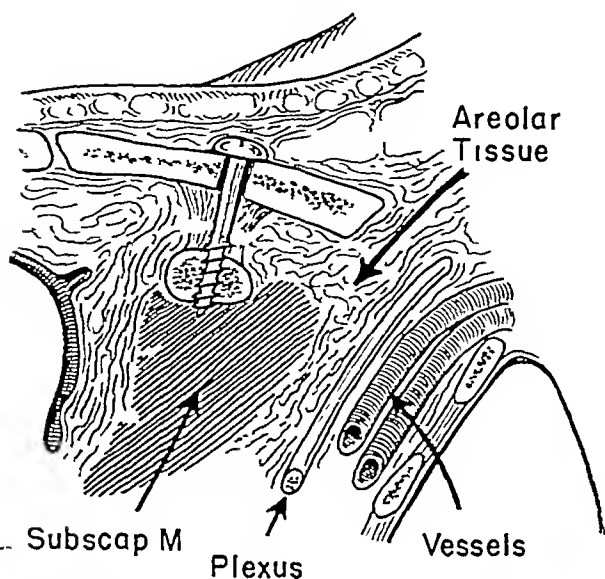
The various nonoperative and operative methods of treating complete acromioclavicular dislocation are reviewed, and their merits and faults discussed and their end results presented. Screw suspension appears to be the simplest, safest and surest procedure thus far devised for this disabling lesion.

44 Pondfield Road

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erated on successfully. My first 10 patients have now been followed personally for four months to seven and a half years (Fig 4). In 8 the result is rated as excellent, with no deformity or pain, with a full range of active and passive motion and with normal strength. One patient obtained an excellent result of the acromioclavicular repair but has some limitation of abduction from a surgical-neck fracture



Screw Suspension, which Maintains the Torn Ends of the Acromioclavicular Ligament in Apposition Until Healing Re-establishes Ligamentous Support

on at the acromioclavicular joint is preserved because the hole drilled in the clavicle is larger than the screw shaft

of the humerus on the same side, subsequently incurred. It is interesting to note that, although the later injury was severe enough to fracture this patient's humerus, the acromioclavicular joint did not redislocate. In an early case in which complete reduction had not been obtained at the time of operation the thin screw that was then being used broke at a later date and redislocation occurred. This patient refused reoperation.

An additional 8 cases operated upon by six other surgeons, with follow-up periods of one month to four years, were reported earlier this year.¹¹ Seven of these patients had excellent results, and there was 1 failure. The known end results, therefore, in 38 cases operated upon by ten different surgeons were good in 36, with failure in 2.

DISCUSSION

It must be admitted that satisfactory results are sometimes obtained by nonoperative treatment.^{24-26, 27-28, 29} However, externally applied restrictive dressings are uncomfortable to wear, they require constant supervision and adjustment, they involve a protracted disability and in many

cases operative intervention is eventually required. In my experience, certain nonoperative methods, such as adhesive strapping, Velpeau dressings and figure-of-eight bandaging, are utterly ineffective in maintaining reduction of a complete dislocation and should not be used.

Most experienced clinicians prefer some form of surgical operation in the treatment of this lesion. The specific procedure chosen will vary with the individual experience and prejudices of the surgeon. Excision of the outer portion of the clavicle and fusion of the acromioclavicular joint both seem to me unphysiologic and unnecessarily radical. After excision of the end of the clavicle most patients experience easy fatigue and weakness in the operated shoulder as compared with the normal, and there is a certain amount of displacement of the affected shoulder.²⁵ This is to be expected when the strut-like support of the clavicle is removed. Fusion of the acromioclavicular joint, by completely eliminating joint motion, necessarily interferes with full shoulder function, especially abduction, as has been proved experimentally.⁵

I consider it far better to preserve the acromioclavicular joint and to restore its function by one



FIGURE 4 *Excellent Function More than Seven Years after Screw Suspension for Complete Right Acromioclavicular Dislocation*

The screw is still in place

of the reparative methods described above. Skeletal traction is the least desirable of these, owing to the risk of infection. Syndesmopexy and ligamentoplasty are major operations. They require a general anesthetic, hospitalization for one or two weeks and a prolonged period of disability and rehabilitation. An additional objection to syndesmopexy is that wire or silk sutures tend to cut through living bone by pressure necrosis when subjected to constant strain over a period of time.

One must face the fact that the majority of these injuries are treated by the general surgeon and that most surgeons will see only a few such cases during all their years of practice. Therefore, a technically

simpler operation is to be preferred, if its results are comparable to those of the more radical procedures

There are certain disadvantages inherent in wire transfixion-fixation. The acromioclavicular joint is completely immobilized, with consequent limitation of motion, for eight weeks. Two operations are required, for the wires must be removed. Wires that have migrated from the shoulder have had to be removed from the neck and even from the lung.⁶¹

The method of screw suspension is free of these objections. Mobilization of the upper extremity is assured from the day of operation. In fact, most patients feel so well that it is difficult to keep them from overdoing. In only the exceptional case need the screw ever be removed. I know of no case in which a screw has migrated to another part of the body. The operation is physiologically sound, suspensive reinforcement is provided at the exact point where it is required anatomically and functionally—and without fixation. No important structures are endangered by the screw.

SUMMARY

The various nonoperative and operative methods of treating complete acromioclavicular dislocation are reviewed, and their merits and faults discussed and their end results presented. Screw suspension appears to be the simplest, safest and surest procedure thus far devised for this disabling lesion.

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NOCARDIOSIS

Pneumonia and Empyema due to *Nocardia Asteroides*

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IN 1888 Nocard¹ described an acid-fast sporothrix, *Actinomyces farcinicus*, as the cause of *farcies du boeuf*, or bovine farcy. Eppinger,² in 1891, reported an aerobic, gram-positive, acid-fast actinomyces as the etiologic agent in a man dying with cerebral abscesses and meningitis. Since then the species of actinomycetes having acid-fast properties has been known as *Streptothrix eppingeri*, *S. asteroides*, *Oospora asteroides*, *Actinomyces asteroides*, *Nocardia gypsoidea* and more recently *N. asteroides*.

The literature on infections caused by this organism is not voluminous and indicates that cases are not common. The diagnosis in the great majority of cases was made only at autopsy or in the late stages of the illness. Furthermore, in the 37 cases reported, only 6 patients are known with any certainty to have survived. One of these was a case of Madura foot treated by amputation of the extremity.

Henrici and Gardner,³ in 1921, collected 26 cases of acid-fast actinomycetes and added a case. Most of these cases apparently were of pulmonary origin. In the case reported the patient was treated with an antigen made from the cultures. The final results of this treatment are unknown. Goldsworthy,⁴ in 1937, and Kessel and Goolden,⁵ in 1938, reported fatal cases. Benbow, Smith and Grimson,⁶ in 1944, described 2 cases in which surgical drainage, vitamin therapy, roentgen-ray therapy and sulfonamide therapy were used. These were the first reported cases in which the patients are known to have recovered except for the one treated by amputation. In 1945 Binford and Lane⁷ discussed a case diagnosed at autopsy. Kirby and McNaught,⁸ in 1946, added 2 more fatal cases. In 1946 Shaw, Holt and Ray⁹ reported a case successfully treated with penicillin, thymol, potassium iodide, sulfadiazine, and surgical drainage of an empyema cavity. In the same year Calero¹⁰ described a twelve-year-old white girl who was considered cured after therapy with sulfonamides and penicillin, but who at the time of dismissal still had an elevated sedimentation rate.

Glover et al.,¹¹ in 1948, summarized the literature and reported in detail the case of a twenty-six-year-old physician in whom the diagnosis of nocardiosis was established more than two years after the onset of his illness. He was considered successfully treated

by sulfadiazine after penicillin and streptomycin had failed. The authors believed that if the case of Madura foot cured by amputation and the case treated with antigen in which the final outcome was not known were excluded, only 5 of the 37 known cases could be considered clear-cut examples of recovery. They attributed the success in these cases to the administration of sulfadiazine. On the basis of their studies and those of Drake,¹² they doubted whether penicillin or streptomycin was effective in the treatment of this disease.

The first case of *N. asteroides* infection reported below failed to respond to sulfadiazine, penicillin or streptomycin until surgical drainage of an empyema cavity was instituted and until these antibiotics were used in combination and in large doses. This combined therapy apparently resulted in complete recovery, since the patient was free of symptoms and signs twelve months after discontinuance of all therapy. The case is of further interest in that the diagnosis was established early in the course of the illness.

A second case of pulmonary infection presumably due to *Nocardia asteroides* has recently been observed. A detailed report of the case is not presented, but results of the sensitivity tests of the organism to sulfadiazine, penicillin, streptomycin and aureomycin are reported.

CASE REPORT

CASE 1 O. M., a 16-year-old schoolgirl, had been well and active during the year prior to her present illness except for an upper respiratory infection, which had occurred 2 months earlier and which had been diagnosed as influenza. On December 24, 1947, she felt feverish and weak, and had pain in the right lower portion of the chest anteriorly. On the following day, the temperature was 100.6°F, and there was splinting of the respiratory muscles on the right side. Posteriorly, the breath sounds were bronchovesicular and diminished, but no rales could be heard. There was a soft systolic murmur at the fourth left interspace. The patient had two episodes of spontaneous epistaxis. Sulfadiazine therapy with equal amounts of sodium bicarbonate was given. On December 28 the temperature had risen to 102.8°F, and the physical signs suggested further extension of the pulmonary lesion, together with findings of free fluid in the right pleural space. There was a cough, which persisted, but sputum was raised on only one occasion. The patient was admitted to the Rhode Island Hospital, where she remained for the duration of her acute illness.

A roentgenogram of the thorax (Fig. 1) on admission to the hospital revealed the heart to be slightly enlarged, but with a normal contour. The left-lung field and diaphragm were normal. The right-lung field showed an area of diffuse density in the lower half through which the diaphragm could be seen faintly. In the lateral half of the right upper portion of the chest there was a large, localized area of density believed to represent an encapsulated collection of fluid in the pleural space.

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The urine was normal. Examination of the blood showed a red-cell count of 3,500,000, with a hemoglobin of 11.8 gm, and a white-cell count of 13,850, with 77 per cent neutrophils, 11 per cent lymphocytes and 12 per cent monocytes. The blood urea nitrogen was 9 gm per 100 cc. A blood culture on December 28, 1947, and numerous subsequent cultures were sterile. A sputum culture revealed *Streptococcus viridans* to be the predominating organism. No acid-fast organisms were seen.

In summary, the only abnormal physical findings were those pertaining to the pulmonary lesion and the general febrile reaction. The patient clinically did not appear as ill as would be expected in a pneumococcal pneumonia, and another etiologic agent was suspected.

The patient was given 100,000 units of crystalline penicillin intramuscularly on admission, and 50,000 units every 3 hours. On the 2nd hospital day the temperature was normal but subsequently it rose irregularly each day for the next few weeks. On December 30 aspiration of the pleural space was attempted posteriorly and anteriorly, but only 2 cc of sterile bloody fluid was obtained. On January 6, 1948, a second aspiration high in the axilla in the third interspace resulted in 20 cc of sterile serosanguineous fluid. After each aspiration, 100,000 units of penicillin was instilled. A roentgeno-

gram of streptomycin, totaling 1.8 gm a day, were instituted. The patient continued to have a dry, hacking cough, but her general condition was good despite the prolonged fever. At this time the signs in the axilla had cleared, but there continued to be dullness to percussion and diminished breath sounds posteriorly. On January 20 the temperature rose to 104°F, and roentgenograms (Fig 2) showed a new dense shadow in the right lower portion of the chest posteriorly consistent with encapsulated fluid. There was a smaller loculation of fluid in the upper peripheral portion of the chest. On January 21 a diagnostic thoracentesis was performed, and free-flowing, foul-smelling, pea-green fluid was withdrawn. Smears

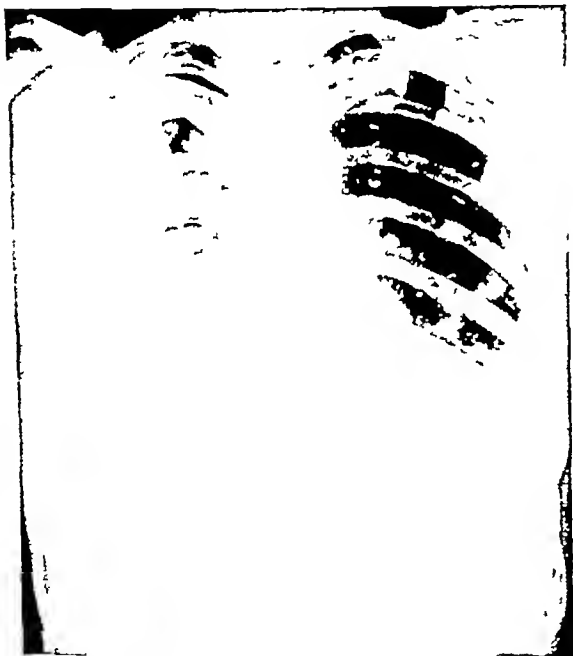


FIGURE 1 Roentgenogram of the Chest Taken on Admission in Case 1

gram of the chest on January 6 showed considerable clearing of the density in the lower-right-lung field, and the encapsulated fluid in the right upper portion of the chest was much smaller in amount. A small quantity of fluid was present in the right costophrenic sulcus.

On January 8, the penicillin was discontinued despite the persistence of slight elevations of the temperature to 99.8°F daily. Roentgenograms continued to show clearing of the pneumonic process and lessening of the free fluid. On January 15 the temperature spiked irregularly to higher levels reaching 101°F daily, and penicillin therapy was again instituted. This elevation of temperature was interpreted as being due to the formation of a loculated empyema. The right leaf of the diaphragm was elevated, and the mediastinum was shifted slightly to the left. Penicillin was omitted 4 days later after no improvement, and intramuscular injections



FIGURE 2 Roentgenogram of the Chest Taken on January 21, 1948, in Case 1

and cultures of this fluid revealed a gram-positive, acid-fast, branching, aerobic organism identified as *A. asteroides*, and gram-negative anaerobic fusiform bacteria.

On the same day a rib resection and open drainage of the empyema cavity were performed, and a large rubber tube was left in place. The cavity was narrow and lined by dense fibrous tissue, which obliterated the surrounding pleural space. It had been entered at the lowest point and dependent drainage was obtained. Antibiotic therapy was increased so that 500 mg of streptomycin and 500,000 units of penicillin were given intramuscularly every 6 hours. Sulfadiazine, 6 gm a day, was begun, the dosage later being increased to 9 gm a day. Sodium citrate was used to alkalinize the urine. Potassium iodide was given by mouth, 500 cc of whole blood was given on two occasions.

Sensitivity tests revealed this strain of *A. asteroides* to be inhibited by concentrations of between 0.004 and 0.008 units of penicillin per cubic centimeter, 0.03 and 0.06 units of streptomycin per cubic centimeter, and 0.62 and 1.24 mg of sulfadiazine per 100 cc. The blood levels of sulfadiazine ranged from 7.0 to 17.3 mg per 100 cc. of free sulfadiazine and from 7.3 to 18.8 mg per 100 cc. of total sulfadiazine. No hematuria or toxic effects from the sulfadiazine or penicillin were noted. On the 27th day of streptomycin therapy, the patient complained of slight dizziness, and when she walked with her eyes closed she staggered considerably. This staggering when visual control of balance is eliminated has persisted ever since, although the Romberg test is nega-

tive and there is no disturbance of gait with the eyes open. No loss in auditory sensitivity has been detected. Streptomycin was discontinued immediately on the appearance of toxic signs after a total of 567 gm had been given. On February 25 penicillin, sulfadiazine and potassium iodide were omitted, and no further antibiotic therapy was administered. The patient received a total of 76,600,000 units of penicillin intramuscularly, 10,700,000 units of penicillin intrapleurally and 288 gm of sulfadiazine orally.

After surgical drainage, the temperature fell to normal and remained so. The operative wound remained clean, and the cavity closed rapidly with little drainage. 500,000 units of penicillin was instilled daily as long as the cavity was open. The tube was removed 21 days after the operation. Iron therapy, in addition to the transfusions, was given for the mild hypochromic anemia. The white-cell count at the height of the illness reached 15,000, with 80 per cent neutrophils. After administration of streptomycin the eosinophils rose from 0 to 42 per cent, whereas the white-cell count returned to a normal of 8050. The sedimentation rate remained elevated until 2 weeks after discharge from the hospital but has subsequently been normal. The cultures of the fluid from the empyema cavity became sterile immediately after surgical drainage of the cavity, but acid-fast, branching rods were seen in the fresh smears 9 days later. The roentgeno-

consistently negative for tubercle bacilli but from which *N. asteroides* was isolated as the predominating organism on several occasions. The patient was afebrile during a short period of observation at the Rhode Island Hospital.

This strain of *N. asteroides* was found to be inhibited by concentrations of between 0.015 and 0.03 units of penicillin, 0.12 and 0.24 units of streptomycin and 0.5 and 1.0 unit of

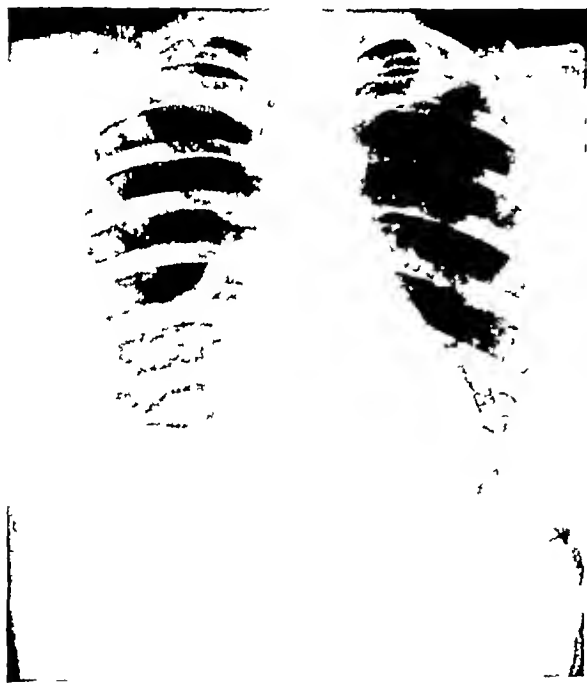


FIGURE 3 Final Roentgenogram of the Chest Taken since Discharge in Case 1

grams of the thorax taken since discharge have shown complete clearing of the pulmonary lesion (Fig 3).

CASE 2 E. H., a 64-year-old woman, entered the hospital with a history of chronic cough of 3 years' duration, attacks of respiratory distress diagnosed as bronchial asthma and episodes of fever associated with pulmonary difficulty. An x-ray film of the thorax revealed (Fig 4) bilateral apical pulmonary lesions. The film was interpreted as showing a moderate amount of fibrotic streaking involving the entire apical portion of the right upper lobe and a number of discrete, calcific deposits in the apex of the left upper lobe. Small calcified nodules were present in the upper portion of the right hilus. No definite cavitation could be made out. The cough was productive of thick, greenish sputum, which was



FIGURE 4 Roentgenogram of the Chest in Case 2

streptomycin per cubic centimeter, but was not inhibited by 60 milligrams of sulfadiazine per 100 cc of medium.

BACTERIOLOGY

The *Nocardia asteroides* organism appears in Ziehl-Neelsen stains of smears made from fresh purulent material as short branching or single rods that are definitely acid fast, however, smears made from the primary culture of the clinical material show partially and irregularly acid-fast elements, and in addition to branching and rod forms there are fine mycelial filaments, some of which fragment into coccoid conidia (Fig 5). With continued transfer on artificial mediums, the organism tends to lose the acid-fast property. This is particularly true when acid alcohol of the Ziehl-Neelsen technic is used to decolorize, however, by the use of a weak solution of sulfuric acid to decolorize, acid-fast elements may be observed in spite of several transfers on artificial mediums. Different strains of the organism show varying degrees of acid fastness, and the cells of old cultures tend to show more irregularity in this regard.

The organisms are gram positive, but, as is true with most gram-positive species, they tend to lose

the property upon aging so that old cultures become gram-negative.

Nocardia asteroides grows well on routine blood-agar and Sabouraud's mediums under aerobic conditions at 37°C. Colonies appear rapidly, within twenty-four to forty-eight hours, under these conditions and show a dry wrinkled growth, which adheres to the surface of the medium (Fig 6). The surface of the colony develops a chalky white appearance, whereas the portion in contact with the medium shows varying degrees of pigmentation, tan to deep orange. In poured plates the organism grows in small star-like colonies, which suggested the species term "asteroides." The pigmentation and morphologic appearance of the colonies vary with the mediums used and the age of the culture, hence the duplication of names appearing in the literature for this species. The usual sodium hydroxide method for concentration of sputum for tuberculosis destroys *N. asteroides* so that animal inoculations and cultures show no growth of the nocardia organism. The weak or semi-acid-fast property may not be noted when routine decolorization of the Ziehl-Neelsen stain is done and the

cellular fibrous tissue, fibrin, neutrophils, lymphocytes, plasma cells and macrophages with branching organisms scattered throughout the tissues.³ The lesions differ from the tuberculous process in that there is no caseation, no epithelioid tubercles and no giant cells. The dispersed mycelia may not show up with the usual hematoxylin and eosin stains but can be demonstrated readily with Gram's stain.

Acid-fast actinomycetes occur naturally in the soil. Gordon and Hagan¹² find no features that would

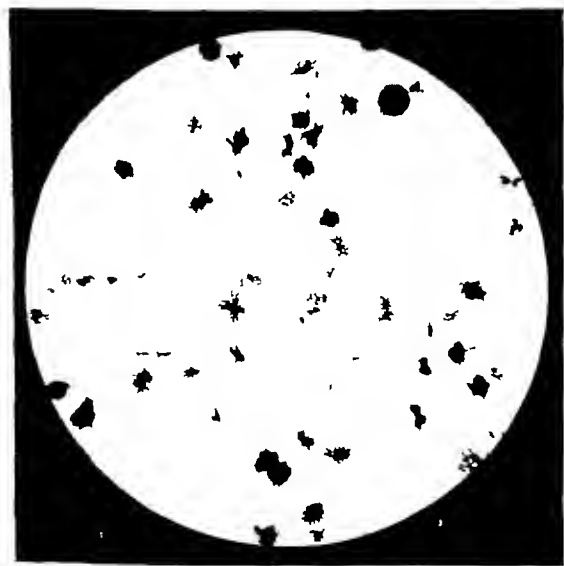


FIGURE 5 Primary Culture of Smear, Showing *Nocardia asteroides* (Ziehl-Neelsen Stain)

acid alcohol is allowed to remain too long on the smear. These facts may account for the recognition of so few cases.

The tissue lesions caused by *N. asteroides* differ from those in actinomycosis in that clubbed forms are not produced, nor are nodules or "sulfur granules" formed. The typical lesion is an abscess whose center is composed of necrotic material and leukocytes. Surrounding this material there is an area of dense

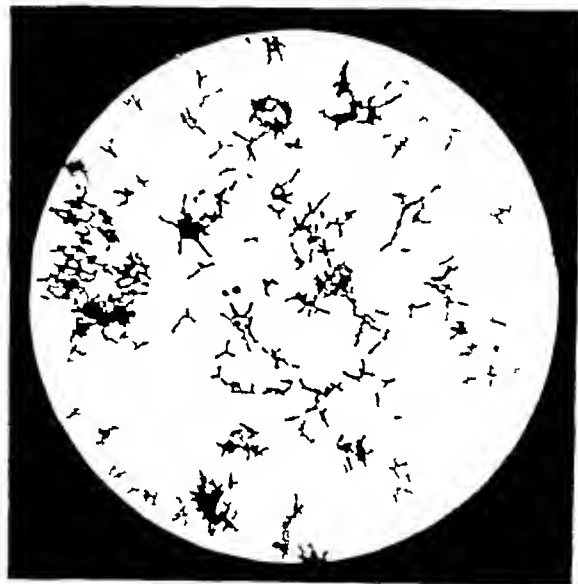


FIGURE 6 Blood-agar Plate Showing Colonies of *Nocardia asteroides*

serve to distinguish these soil forms from the pathogenic stains. A similar organism was isolated from a normal throat in 1 case.¹³ Rabbits, guinea pigs and other laboratory animals are fairly resistant to infection with strains that cause disease in human beings.

The development of an allergic reaction can be demonstrated in animals after intratesticular injection of an oil suspension of the live organisms and the use of cutaneous tests. Protein extracts of the organisms cause a swollen area with central necrosis. The allergens are thermolabile and appear to be specific with no cross reactions with tuberculin.¹⁴ By using 0.5 cc of a crude extract of unheated, defatted organisms passed through a Berkefeld filter candle, Glover et al.¹¹ demonstrated positive intracutaneous reactions in twenty-four to forty-eight hours in their patient.

DISEASE IN MAN

The great majority of cases reported indicate that the infection usually begins in the lung, or

that a pulmonary metastasis from some other focus occurs early in the disease. The pulmonary lesion may remain quiescent or asymptomatic for some time, since the metastatic blood-borne secondary abscesses are frequently the ones to be noted first or to cause symptoms. The pulmonary lesions frequently extend to the pleuras, giving rise to an empyema that may form chronic draining sinuses to the chest wall. Of the metastatic lesions, brain abscesses have frequently been noted, and have most often been the lesion causing death. In some cases positive blood cultures have been obtained.⁸ Subcutaneous abscesses are frequently encountered, and the skin may be involved. Some of the cases examined at autopsy have revealed multiple miliary abscesses in many of the organs of the body, such as the brain, liver, spleen, kidneys, adrenal glands, intestinal wall, lymph nodes and muscles.

The most frequently encountered symptoms were anorexia, weight loss, weakness and a chronic cough, which as the disease progressed became productive of foul, greenish, purulent sputum. Hemoptysis was rarely encountered, and cavitation was not usual. In some cases, pulmonary signs and symptoms were completely lacking, and the patients came to medical attention because of the neurologic signs of an intracranial abscess or because of abscesses or draining sinuses. The disease is most easily confused with tuberculosis, and when the illness is localized to a chronic pulmonary infection the true diagnosis may not be established for many months. Two cases of peritonitis have followed operations on the esophagus. The patients in the cases reported have been of all ages from an infant twenty-eight days old to elderly people. The division between the sexes has been approximately equal. The pulmonary lesions may occur in any lobe, and there is often early involvement of the peribronchial lymph nodes. A hypochromic anemia was frequently observed to develop as the infection persisted. Some of the patients died within two weeks of the onset of symptoms, whereas in others the infection was active for at least three years. The average duration of the fatal cases was six months. In every case the diagnosis must be made by bacteriologic study, but it should be suspected in all cases of pulmonary lesions in which the tubercle bacillus cannot be demonstrated or when miliary abscesses are encountered.

TREATMENT

The literature is of little value as a guide to treatment. Prior to the use of the antibiotics, the iodides and thymol were the usual agents and no patients survived. The authors of the reports of the few successfully treated cases are not in full agreement concerning the procedure or drug of choice. When possible the sensitivity of the organism at hand should be tested, and the antibiotics that are effective in inhibiting it should be utilized either alone

or in combination. Of the sulfonamides, sulfadiazine or sulfamerazine seems to be the most active and the least likely to cause toxic reactions. When these drugs are utilized the urine should be alkalinized with sodium bicarbonate or sodium citrate. Penicillin in large doses — or by the utilization of some medication such as caronamide to achieve a sufficiently high blood level to inhibit the organism — seems to be the safest drug available. In the case reported by Glover and his associates,¹¹ the organism was not inhibited by 100 units of penicillin per cubic centimeter of medium. Streptomycin in sufficient concentration inhibits the organism in vitro, but the possible toxic effects on the eighth cranial nerve, with permanent impairment of hearing and the equilibrium mechanism, must be fully appreciated, and the danger accepted. This toxicity, it is now realized, may occur early in therapy and even with small or moderate dosage. Whether dihydrostreptomycin hydrochloride or aureomycin is equally effective in vivo against this organism is not known. The second strain isolated by us was inhibited readily by aureomycin in vitro. It is sound surgical practice to remove by surgical drainage or by aspiration any collections of purulent material. Instillation for local action of the antibiotics is believed to be helpful. In any event, it is necessary to observe the patient carefully for several years for a recurrence, for in 1 case⁹ a reactivation of the infection occurred eleven months after all symptoms and signs had abated.

SUMMARY

The pertinent literature in infections with the acid-fast aerobic actinomycetes *Nocardia asteroides* is reviewed. The characteristics of the organism and of the infection in man are given in brief. A case of pulmonary infection complicated by empyema in a sixteen-year-old schoolgirl is presented. This case was apparently successfully treated by surgical drainage and combined therapy with sulfadiazine, penicillin and streptomycin.

A second strain of *N. asteroides* was isolated from the sputum of a sixty-four-year-old woman with bilateral apical pulmonary lesions. This organism by in vitro tests was found to be inhibited by penicillin, streptomycin and aureomycin, but not by sulfadiazine with levels that usually can be attained clinically when adequate dosages of these antibiotics are administered.

Failure to recognize *N. asteroides* as the etiologic agent in certain infections may account for the scarcity of cases reported. Such failure may be due to the way in which routine specimens of sputum are prepared for inoculation or examination. It is stressed that large doses of the antibiotics to which the organism is sensitive may have to be given and that it may be necessary to administer combinations of two or more in order to obtain prompt inhibition of the organism. Surgical drainage or as-

piration of loculated collections of pus is believed advisable for early healing. Observation for a period of years after apparent arrest of the condition is advisable.

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ORTHOXINE IN BRONCHIAL ASTHMA* A Clinical Evaluation

IRVING W. SCHILLER, M.D.,† FRANCIS C. LOWELL, M.D.,‡ WILLIAM FRANKLIN, M.D.,§ AND CLARENCE DENTON, M.D.¶

BOSTON

SINCE the elucidation by Chen and Schmidt¹ (1923) of the chemical structure and the pharmacologic effects of ephedrine, this drug has ranked with epinephrine as one of the most valuable medications for the treatment of bronchial asthma. Although less active as a bronchodilator than epinephrine, ephedrine is effective, and its action is prolonged. However, undesirable effects such as nervousness, tremulousness, sleeplessness, vertigo, sweating, anorexia, nausea and palpitation often interfere with the use of the drug or require the additional administration of sedatives. In the last few years, therefore, attempts have been made to produce sympathomimetic compounds with less effect on the cardiovascular and central nervous systems. One of these, orthoxine,|| orthomethoxy- β -phenylisopropyl methylamine hydrochloride (Fig. 1), appears to have certain advantages over ephedrine.

In animal experiments orthoxine was found to be more effective than ephedrine in relieving bronchial spasm induced by histamine, pilocarpine and acetylcholine.^{2,3} It caused practically no pressor response

and less stimulation of the central nervous system than ephedrine.⁴ In man, orthoxine has furnished protection against asthma-like attacks induced with histamine or methacholine.^{5,6}

MATERIALS AND METHODS

Fifty patients with bronchial asthma, about equally distributed between the sexes and ranging in

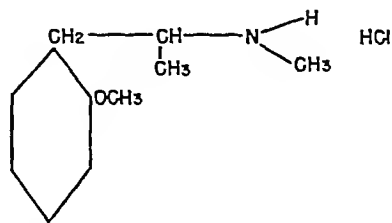


FIGURE 1 Chemical Structure of Orthoxine

age from four to sixty-three years (the majority being adults), served as subjects for this study. The perennial type of asthma predominated. Some patients were receiving treatment with specific allergenic extracts, and many of them had been instructed to eliminate offending allergens. All subjects were having mild to severe asthma at the time treatment with orthoxine was started, and they were observed for a period of weeks to several months. The dose varied from 50 mg. in children to

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100 or 200 mg in adults, given every four hours as needed. Control studies with placebos were used in some cases, and no benefit was observed. Relief of symptoms, when it occurred, was evident in twenty to thirty minutes. The results were classified as follows: excellent, if complete relief of symptoms occurred for several hours; fair, if relief was 50 per cent or more and lasted two or more hours; and unsatisfactory, if the relief was less than 50 per cent or if the duration of activity was short.

RESULTS

As shown in Table 1, 18 (36 per cent) patients had excellent relief, 17 (34 per cent) obtained fair relief, and the remaining 15 (30 per cent) had unsatisfactory results. On the basis of the degree of asthma, patients with mild asthma fared best, followed by

TABLE 1 *Therapeutic Response to Orthoxine*

DEGREE OF ASTHMA	NO OF CASES	EXCELLENT RELIEF	FAIR RELIEF	UNSATISFACTORY RELIEF
		NO OF CASES	NO OF CASES	NO OF CASES
Mild	14	7	6	1
Moderate	21	10	7	7
Severe	15	1	4	7
Totals	50	18	17	15

those with cases of moderate severity. Those with severe asthma obtained the least relief.

Prior to the administration of orthoxine 28 patients had been taking ephedrine in one form or another or, having previously taken orthoxine, had substituted ephedrine. In this way we were able to gather some impression of the relative value of the two drugs, taking into account the degree of relief as well as the intensity of side reactions, discussed in detail below. Ten patients preferred orthoxine to ephedrine. In 2 there was no advantage in one drug over the other, whereas the remaining 16 preferred ephedrine to orthoxine.

In 4 patients, substitution of orthoxine for ephedrine was advantageous. Marked side effects with ephedrine developed in 3, and 1 of these had hypertension. In this patient and in a fourth, who had a recent coronary infarct, it was believed that ephedrine, because of its pressor effects, should not be given. All 4 of these patients tolerated orthoxine well and obtained excellent relief.

Observations were made in asthmatic subjects to determine the degree to which orthoxine could protect against asthma-like attacks and a fall in vital capacity following the inhalation of aerosolized allergenic extracts.⁷⁻⁹ Three patients, all of whom had been tested in this manner and had had significant pulmonary reactions following inhalations of nebulized extracts (5 per cent birch pollen in 2 cases and 0.25 per cent Endo house dust in the remaining one) were chosen for this study. In brief, the patients came to the laboratory when free of asthma and in a

fasting state. Three or four control vital capacities were recorded, after which 200 mg of orthoxine was given by mouth. At the end of an hour the subjects were again tested with the nebulized extracts that had previously caused significant reductions in vital capacity. In no case did orthoxine protect the patients, the pulmonary response being almost identical with that experienced without the drug. Although this technic has been valuable in assaying drugs given parenterally or by inhalation,^{8, 10} administration of drugs by mouth has not given clear inhibition of asthma-like attacks induced with aerosolized allergenic extracts. This may be due to the lack of refinement of the method or to the relatively heavy exposure of the inhaled extract, which may mask slight or moderate activity of the drug. The lack of protection by orthoxine is of doubtful significance and is in contrast to the reported efficacy of this agent given by mouth in affording some degree of protection or relief in asthma-like attacks induced with histamine or methacholine given parenterally.⁶

SIDE EFFECTS

Of the 50 subjects with asthma, 43 (86 per cent) were completely free from unpleasant side reactions. Of the remaining 7 (14 per cent), 4 had gastric disturbances as follows: questionable nausea in 2, nausea in 1, and nausea and vomiting in 1. The last patient was an eleven-year-old boy in whom the same symptoms likewise developed after the taking of ephedrine. Of the other 3 cases, 1 patient had menstrual-like cramps, 1 reported dizziness and sleeplessness, and 1 excessive perspiration. Four of these 7 patients with side reactions obtained little or no relief from orthoxine, so that the drug was discontinued. The remaining 3 had excellent or fair relief of asthma upon decrease in the dose of the drug to 50 mg, or, as in 1 case, when the drug had been withheld for a few days and was again given.

DISCUSSION

The difficulty of judging the effectiveness of an oral preparation for use in bronchial asthma is recognized. Patients have a tendency to overestimate the benefits of any new drug when it is first used. Nevertheless, we believe that our impression of orthoxine is fairly well founded.

The response of 27 out of 35 patients with mild or moderate asthma was excellent or fair with orthoxine, which compares favorably with other well known oral sympathomimetic agents. Similar results with orthoxine were recently reported by Wittich.¹¹ However, the majority of our patients in whom comparison was possible, preferred ephedrine to orthoxine. In the 15 patients with severe asthma, the drug was relatively ineffective. In most cases, these patients obtained relief with other medications such as epinephrine, isuprel and aminophyllin. Our experience is not entirely in accord with the findings of

Curry, Fuchs and Leard,⁶ who, in their clinical studies on 21 asthmatic subjects, observed orthoxine, in doses of 200 mg, to be comparable to ephedrine in 30-mg doses. This discrepancy may be accounted for, in part, by the fact that we often used smaller doses of orthoxine and usually gave ephedrine with a barbiturate.

We are aware that results similar to those obtained with orthoxine might have been obtained with other preparations for asthma. However, the figures cited in Table 1 do not indicate the true value of a preparation such as orthoxine because they leave out of account reactions of individual patients. For instance, more patients may obtain relief from asthma with ephedrine than with orthoxine, as in the cases discussed above but in certain patients who may be unable to tolerate ephedrine, orthoxine may give relief and may be well tolerated. We believe, therefore, that orthoxine is a valuable addition to the list of agents available for the treatment of asthma.

SUMMARY

Fifty patients with bronchial asthma were treated with orthoxine-orthomethoxy- β -phenylisopropyl methylamine hydrochloride. The drug is an effective oral sympathomimetic agent especially applicable to the milder cases of asthma.

Although it did not appear to be quite as effective as ephedrine, orthoxine had the advantage of causing less disturbance of the cardiovascular and central nervous systems. It is concluded that orthoxine is a distinct contribution to the management of bronchial asthma.

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CLINICAL OBSERVATIONS CONCERNING SCHIZOPHRENIC PATIENTS TREATED BY PREFRONTAL LEUKOTOMY*

JAY L. HOFFMAN, M.D.†

BEDFORD, MASSACHUSETTS

IT IS my purpose here to consider the clinical results of leukotomy in 42 patients treated by psychosurgery‡ at a Veterans Administration hospital during a two-year period — 1947 and 1948. To prepare for this I have reviewed the clinical records of these 42 patients and, within the past two weeks, have examined those who remained in the hospital. I have also gone over the social-service reports of the patients who have left the hospital and, in a few cases, have interviewed the relatives myself.

I am less concerned in this report with statistics than I am with the qualitative results following leukotomy. Therefore, the only figures that I will give are as follows: of the 42 patients operated on 4 (9 per cent) are now dead§, 14 (33 per cent) are

out of the hospital — either discharged or on extended trial visit, 16 (38 per cent) are still in the hospital, although so far as behavior is concerned they could live at home equally well, and 8 (19 per cent) are still in the hospital and require hospital care because of continuing episodic disturbed behavior.

The evaluation of the results after prefrontal leukotomy will be greatly influenced by the frame of reference one uses. If the condition of the patient is compared with his condition prior to the onset of his psychosis, all the results must be considered failures, for the adjustment of none of the patients — when viewed with true objectivity — compares favorably with the prepsychotic status. If the clinical status after leukotomy is compared with the condition of the patient during the period of his psychosis, practically all the patients, who have survived will be found to show successful results. From the quantitative viewpoint none of the patients, after

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leukotomy, manifest the extreme of unacceptable behavior found before the operation •

The evaluation of this procedure is made uniquely difficult and rather arbitrary by another factor, and that is that the one most directly concerned with the treatment — the patient — has not participated actively in the evaluation of the results. The opinions of the relatives and of the doctors and the nursing staff concerning this procedure are known, but I must confess that the opinion of the patient himself is not known. For, in practically every case, the patient, when questioned, professes not to know anything about any surgical procedure to which he has recently been subjected. This is particularly true when the patient, postoperatively, shows a great deal of dullness, indifference and apathy. Patients who do recognize, as indicated by their replies to questions, that an operative procedure has been carried out on the brain seem to have little or no understanding of the operation or the results to be attributed to it.

Before proceeding farther I wish to make note of the fact that the group of patients under consideration were, with 1 exception, schizophrenics whose illness and hospitalization was of two to twenty years' duration at the time of operation. The results may therefore not be directly comparable with the series of results reported for nonschizophrenic patients, or for schizophrenic patients whose illness has been of relatively brief duration.

Those who have participated in the selection of these patients for leukotomy, or who have had them under care before the operation, are familiar with the preoperative clinical picture. There are no significant exceptions in any of the 42 patients so far as the characteristics mentioned below are concerned. For those who are not familiar with their preoperative clinical picture I may say that, with one exception, they have all been schizophrenics hospitalized for two years or more — generally five years or more. The male patients, for the greatest part, were resident in the building for the most disturbed patients. They were, before operation, excited, assaultive, combative and destructive. Most were hallucinated and deluded and, characteristically, appeared to be tortured, agonized and distressed beyond measure by their morbid mental experiences. Most had made one or more suicidal attempts, and most had required, for greater or shorter periods, mechanical restraint, chemical restraint or seclusion. With but 1 or 2 exceptions, their previous treatment had included convulsive therapy or insulin-shock therapy or both. Most had not been outside a mental hospital for two years, five years or — in 1 case — about twenty years. Their children had forgotten them. Their wives and parents had, in many cases, adjusted their lives so as not to include the patient in their present or future reckonings. By all criteria that are now

known, the future for these patients offered only a continuation of the recent past.

This, then, is a composite clinical picture of the patients in the series before operation. Regarding the postoperative results I wish first to consider the group of patients who are still in the hospital.

Taking one of this group in whom the result is rather more favorable than most, I will arbitrarily select the order and emphasis to be given to the clinical features in the case. This patient is now neat in personal appearance and tidy, eating and sleeping well. The reports of the nurses indicate that, at various times, he attends dances, goes swimming, listens to music, views television shows, goes bowling, reads and visits the occupational-therapy shops. He works on the hospital chicken farm, where he gathers eggs, feeds and waters chickens and cleans the chicken house. When interviewed by me, he stated that he felt relaxed and was no longer hallucinated or delusional, he recalled, without much show of concern, his rather prolonged stay, before his operation, on a ward for disturbed patients. He remembered that it was noisy there and that he could not read. He is polite in his manner today, and answers questions promptly but slowly. He is correctly oriented. He has ground privileges. In response to leading questions he tells me that he was operated on in Ward 2-E. "They call it lobotomy. It means cutting the nerves in my head. I woke up and had a bandage on my head. No, I don't see much difference in the way I feel."

To a greater or lesser extent the clinical results described above are to be found in about two thirds of the group of patients remaining in the hospital. If still hallucinated, they are no longer disturbed by these hallucinations. They no longer require restraint or seclusion. They either have ground privileges, go home on short visits, or are able to live in the hospital under conditions involving relatively little supervision. They participate in the activities — movies, dancing, bowling and so forth — that give most people pleasure. Whether these activities give pleasure to the patients under discussion is difficult to determine. For these patients are not only no longer distressed by their mental conflicts but also seem to have little capacity for any emotional experiences — pleasurable or otherwise. They are described by the nurses and the doctors, over and over, as dull, apathetic, listless, without drive or initiative, flat, lethargic, placid and unconcerned, childlike, docile, needing pushing, passive, lacking in spontaneity, without aim or purpose, preoccupied and dependent.

In the evaluation of these results, with what is one to be most impressed — with the contrast between the tormented, assaultive, maniac and the placid, docile, childlike person who goes to dances, reads, listens to music and goes to the movies? This contrast is indeed both marked and

impressive. However, I cannot but recall the remark of the relative of a patient, as reported in an English journal, that the patient seemed to have lost his soul in the process of being changed from one state to the other. I am further reminded of the story about the farmer who made a pact with the devil. Here, however, it is the surgeon, rather than the patient, who appears to have made the pact, and, unfortunately, there is no Daniel Webster to release the patient from his pact.

I should like to consider the patients who have left the hospital and examine more closely the types of adjustment that, in the records, are reported as "satisfactory." These cases are as follows:

M. G. has been home for 1 year and 9 months. During this period he has been married, and his mother reports that he and his wife are very happy together. She further states that if people did not know that the patient had been in a mental hospital they could not tell it by seeing him or talking to him now. The patient, a musician with some talent before the onset of his psychosis, accepted equably, upon his release from the hospital, his rejection as a student by a music school. The school believed that he had not had enough practice in recent years to be able to profit by further intensive training. He went instead to a school of optics and completed the course in a year. There was no job in optical work readily available, and he did not persist in efforts to find employment in his new trade. Instead he got temporary work in the post office. At present he is going to an upholstery school and has been promised a job by his brother, who owns an upholstery shop.

I. R. has been at home continuously for exactly 2 years. His wife, who remained faithful to him throughout the long period of his psychotic illness and visited him regularly in good weather and bad, whether abused by the patient or not, has bought a house with the accumulated retirement pay of the patient as a down payment. She has remodeled the house so that she collects rent for half of it, and this, in addition to retirement pay, is their only source of income. The patient spent 6 to 8 months at the time of release from the hospital at the Boston Community Work Shop, but it was reported that he was unable to learn any trade. The social-service workers have found several jobs for him, which he either refuses or loses before he starts because he insists on informing his prospective employer that he has had half his brain cut out, that he has been in insane asylums for several years, that he is legally incompetent and that his wife holds all his money. He insists on telling obscene jokes in the presence of strangers and in using profanity freely. Last summer, at a local beach, he distressed a woman neighbor because he calmly placed himself in a conspicuous place on the beach where he unabashedly viewed the charms of the women passing by on the boardwalk overhead. The patient's wife calmed the irate neighbor by telling her that her husband did the same thing, except that he did it furtively. According to the wife, the patient has built a picket fence around their property and puts up shelves and builds bookcases around the house. Objective reports are, however, less favorable and indicate that he is slow at any work he undertakes, that his results are poor, that he does not appear to have a care in the world and that nothing seems to bother him. He shows no sense of responsibility and no sense of urgency to assume the role of father and husband. The opinion of the wife concerning the operative procedure is of interest. I asked her whether, if she had it to do over again, she would again give permission for the operation. Her response came without a moment's hesitation and carried with it a note of conviction: "Yes, indeed. Now we have a home together and are a family again."

Another patient, a woman, has been home for 6 months. Still delusional, but not aggressive about her delusions, she is a slovenly housekeeper, with no sense of responsibility to her husband and children. It is only because her husband is a mild, passive man, willing and able to arrange his working

hours so that he can be home much of the day, that she can continue to live outside the hospital.

F. F. has continued to live outside the hospital, but the circumstances under which this has been made possible are significant. Immediately after the operation, his stepmother was hostile to any plans to bring him home, but an aunt agreed to take him in. He was reported as being friendly and cooperative, but without much drive. Like many of these patients, he was described as being "inconsiderate." By this term, it was meant that he left the water running in the bathroom, neglected to close the outer door on cold days and left the radio blaring for hours on end. After a few months of such behavior at his aunt's home it began to appear that his further stay there would not be welcome. About this time he married a girl he had met since his leukotomy. From the fact that his wife is reported to have had a harelip, one would assume that she would be more tolerant than the aunt of one so handicapped as the patient. This has proved to be the case, and in spite of the fact that the patient continues to be unable to hold a job and to be generally irresponsible, he and his wife appear to be happy and contented.

L. F. lives on the farm of his overprotective mother. While he was in the hospital, his mother used to visit me frequently—pleading, cajoling and demanding to take her son home. Now he is her little boy again. He does simple errands, enjoys playing with boys of 7 and 8 years old in the neighborhood, and is himself shy, childish and dependent. He cannot learn to do any but the very simple chores about the farm. His mother, however, is entirely satisfied.

From the report of another patient it is noted that his mother does not care if he never goes to work again because, as she puts it, she is willing to support him for the rest of his life.

Another continues unemployed after 5 months but is otherwise well adjusted at home. Still another lives with an easy-going mother of limited intelligence. The family are pleased to have him home. He goes to the movies but is otherwise without initiative, and is poorly oriented and mildly confused. His mother writes, "He is no good for any job that would pay money."

Another patient helps his brother in his grocery store by sweeping floors and stocking shelves but is not permitted to wait on the customers.

DISCUSSION

It might be desirable to mention a few minor points concerning which interest has been expressed. Since leukotomy may have, as one of its effects, the reduction of inhibition on the part of the patient, the question of postoperative sexual behavior has been raised. From the information derived from this group of patients it appears that there has been no aggressive or objectionable sexual behavior in any of the patients. There have been open masturbation, preoccupation with obscene jokes, and obscene speech and uninhibited staring at female passers-by. One or two female personnel in the hospital have reported being "annoyed" by these patients, without detailing the type of annoyance, but when the patient was spoken to by his physician there was no repetition. The wife of a patient reports that his sexual interests in her are diverted if she simply turns him over in bed so that he faces the wall.

Some of these patients are extravagant with money and seem to have little sense of value. Others are not. Some are extravagant at first but later learn to take care of money.

The inability of patients to learn to carry out any but the most simple tasks, is noted repeatedly by hospital workers. This fact has considerable bearing on the difficulties the patients have in finding and holding employment.

The point about this study that has impressed me most is that not one of 42 patients has been able to make a fully independent social and economic adjustment after operation. None are completely self-supporting. All require a protective environment—either in the hospital or at home—for survival. All have had to borrow something from the ego of a devoted wife, son, mother or sister. These patients as a group remind me of a watch that has stopped. If one shakes it vigorously the watch is apt to tick a few times, and the tick sounds like that of a watch in good repair, but it runs down almost immediately and stops. In fact, I have not been able to wind these patients up sufficiently so that they can run like an eight-day clock, or for that matter, even for a day.

I recognize that in this brief presentation, I have not discussed the contributions and limitations of medical rehabilitation and social-service activities. Important as these topics are, the limited time at my disposal makes such neglect necessary.

In this presentation I have deliberately described at some length what must be considered the less desirable clinical results of leukotomy. I have done

this because most people interested in the subject have been so impressed by the dramatic changes in behavior produced by leukotomy—from a wildly excited, assaultive, combative, suicidal psychotic to a mild-mannered, docile, “well behaved” patient—that they have, perhaps, overlooked the very real and permanent losses to the integrity of the personality. I think it should be re-emphasized that by psychosurgery an organic brain-defect syndrome has been substituted for the psychosis, but the psychosis has not been cured. Psychosurgery, in my opinion, is a temporary therapeutic expedient, justifiable only because knowledge of specific therapy is still not sufficiently developed or available to effect true cures in many of these patients.

It seems to me that one should be hesitant in recommending leukotomy for the chronic schizophrenic patient unless he is chronically assaultive, combative, homicidal or suicidal and his very life is jeopardized by an uninterrupted continuation of this state, or, in selected cases, the return of the psychotic patient to the family circle of a distraught mother or other relative can be justified for humane reasons. The emotional need of such a mother for her son—morbid though it be—can be satisfied after leukotomy of the son, as I have indicated in some of the cases discussed above.

MEDICAL PROGRESS

EXFOLIATIVE CYTOLOGY*

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THE past eight years have witnessed widespread revival of the study of body fluids as an adjunct in the detection of cancer. The focus of attention in these fluids has been on the cellular constituents—the cells that have become separated from body surfaces by the natural process of desquamation. An apt phrase, “exfoliative cytology,” has been coined by Papanicolaou to describe this field of investigation. It is eminently fitting that he should be the one to do so, for Papanicolaou’s original painstaking observations are the firm foundation on which this science has been built.

Sporadic attempts to use exfoliated cells as an indication of underlying disease have been reported in the medical literature of the last hundred years.

The results were confusing and of low accuracy. Then, in 1917, Stockard and Papanicolaou¹ described the first of a long series of observations on the cellular pattern of aspirated vaginal fluid of rodents. The course pursued in these studies and their culmination in the recognition of cells from malignant growths in the human female genital tract is outlined in Papanicolaou’s² review of 1946. From his reports, one conclusion is inescapable and crystal-clear: a high degree of accuracy in the interpretation of exfoliative cytologic preparations is possible only after one is *thoroughly familiar* with the numerous cellular variations that may be found in benign states.

The number of scientific papers on this subject shows a steady increase every month and proper evaluation of each contribution becomes more and more difficult. It may be helpful to epitomize the procedure in outline form in its simplest terms and

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to measure each new report in the light of whatever feature it emphasizes

- 1 Preparation
 - a Collection
 - b Fixation
 - c Staining
- 2 Interpretation

Thus there are two basic steps in any cytologic study—the preparation of a slide and its interpretation. Preparation involves collection of material, fixation and staining. Whatever the method of collection, it must have as its goal the transfer to a glass slide of a representative specimen of cells well preserved and recently shed from the area under investigation. The process of fixation should be able to maintain cellular detail for an indefinite period without destroying or removing an appreciable number of the cells originally present on the slide. Staining and counterstaining should provide sufficient contrast to bring out minute nuclear and cytoplasmic morphology, again without destroying or removing cells in the process.

Interpretation, the second basic step, should be restricted to persons who have received special training for that purpose and who are in a position to improve their accuracy by constant practice. Facility in the recognition of abnormal cells can be developed in no other way, the occasional microscopist cannot hope to do so. With this outline and these fundamental principles in mind, some of the literature on exfoliative cytology is reviewed. This is best done if the body systems are considered separately.

FEMALE GENITAL TRACT

Although a brief note in 1928³ has recorded Papanicolaou's earliest conviction that cancer of the uterus sheds recognizable cells into the vaginal fluid, it was not until 1941 that Papanicolaou and Traut⁴ made a complete report, including both the description of their technic and criteria used in diagnosis. A monograph published in 1943⁵ presents their material in detail. Within a few years Meigs,⁶ in Boston, Jones,⁷ in New York, and Ayre,⁸ in Montreal, reported extensive trial of the method and complete agreement with Papanicolaou's conclusions. These early papers are concerned almost exclusively with the problem of interpretation. All agree that the more experienced the cytologist and the more smears examined on a given patient, the greater the likelihood of finding cancer when it is present. Their cytologic accuracy ranged around 90 per cent for patients with carcinoma of the cervix and between 80 and 90 per cent for cases of carcinoma of the fundus. They pointed out that errors of another type were also encountered, when cytologic reports of malignant lesions that could not be confirmed pathologically were rendered. A number of other clinics⁹⁻¹¹ have now studied the

method and reported their results, no one who has given it an honest trial has condemned it. It should be noted that there is considerable variation in methods of statistical analysis, for some papers list cytologic data and calculate percentages of pathological confirmation, whereas others report cases proved to be cancer and calculate percentages of cytologic accuracy. The Vincent Memorial Hospital group uses only the first cytologic report on each patient in its statistics—a method designed to permit evaluation of exfoliative cytology as a screening procedure.

Almost every publication in this field has included cases in which malignant cells were found in the vaginal fluid and the lesion has proved to be pre-invasive cancer of the cervix (carcinoma-in-situ). This fact is of vital importance and, fortunately, is not dependent on mere chance for a comparison. Between smear and biopsy¹² in a group of 181 proved cases of cervical cancer has demonstrated that each of these methods tends to pick up the lesions that the other one misses. Thus, the smear is of great value in revealing extremely early cancer of the cervix, and in this series, by the use of *both* methods of diagnosis, only 3 of the cases were missed at the time of *first* examination.

The interpretation of the vaginal smear after radiation therapy to the genital tract is a special study in itself. The cellular changes noted under these conditions are described by Graham.¹³ These effects are present in both the normal and the malignant cells. When cases were classified according to degree of radiation response as judged by these cytologic changes, remarkable correlation with their clinical behavior was apparent. Graham concluded that the smear may be of great prognostic value in cases of cancer of the cervix treated by radiation.

It is obvious from Graham's paper that a trained observer can, without great difficulty, recognize malignant cells after radiation or other therapy. Repeated cytologic check on such patients may lead to the discovery of persistent or recurrent disease. Over 10 per cent of Meigs's¹⁴ 1015 cases were patients in the gynecologic tumor follow-up clinic, and one of his protocols describes a case in which smears were consistently positive for nine months before recurrent disease of the cervix could be histologically confirmed.

Failure to achieve 100 per cent accuracy has inevitably led to modifications in the method of preparation of the cytologic specimen. As early as 1943 Papanicolaou and Marchetti¹⁵ described the use of a small cannula to aspirate fluid directly from the endocervix and the endometrial cavity. Ayre¹⁶ also has preferred to collect his material from the region of the external cervical os originally by aspiration and more recently by rotatory scraping with a special wooden spatula. This he calls, quite rightly, a "surface biopsy." Hunter¹⁰ has used the Papanicolaou

technic but also collects surplus vaginal fluid in fixative and sections and stains the resulting pellet in orthodox pathological fashion. Each method of preparation produces its own characteristic cytologic pattern, and each demands experience before accuracy is possible.

There is universal agreement that smears should be fixed *immediately* and not allowed to dry. Ether and alcohol, alcohol alone, Schaudin's solution and others have been used with equal success. Staining is usually by Papanicolaou's¹⁷ method, although some prefer hematoxylin and eosin.

Although the exponents of exfoliative cytology point out repeatedly wherein it deviates from the ideal, it is from the pathologist that one expects constructive criticism. Several articles and a handbook of diagnosis by Gates and Warren¹⁸ and their associates present the attitude of the practicing pathologist. They warn against its use in place of other well established methods of diagnosis and decry any complacency founded on cytologic reports alone. In evaluating its use as a screening test for women without symptoms,¹⁹ they question whether the low yield is economically justified. However, they agree that some cases of cancer are unquestionably discovered earlier by this means than would otherwise be possible, and they point out that these investigations have given desirable impetus to the study of very early cancer.

The dramatic possibilities inherent in the cytologic method have not failed to rouse the interest of writers who attempt to interpret things medical for the public at large. At least two articles^{20, 21} have appeared in women's magazines. The facts presented are scrupulously accurate, but their selection and accompanying text are so uncritical that one is left with the impression that any physician who cannot or will not perform this simple test on his patient is derelict in his duty. Such publicity, unfortunately, creates resentment within the ranks of the medical profession and a bias that will have to be overcome by complete honesty of reporting in professional journals.

PULMONARY TRACT

In 1946 Herbut and Clerf²² reported a series of 30 patients with proved carcinoma of the lung in whom bronchoscopic aspirations or washings were studied by Papanicolaou's technic of fixation and staining. In 22 cases (73 per cent) malignant cells were found. Similar study of expectorated sputum in 7 cases revealed cells only once. No false-positive reports are recorded, but the authors draw attention to 7 cases in which cytologic examination showed cancer although bronchoscopy had failed to reveal a tumor. A more recent summary of Herbut's work shows 105 positive smears in 118 cases of cancer of the lung, an accuracy of 89 per cent. A false-positive report was made in 4 additional cases.

Others have not found the examination of sputum so unrewarding. Papanicolaou²³ noted malignant cells in the sputum of 88 per cent of 25 patients with cancer of the lung, and Woolner²⁴ states that sputum or bronchial secretion proved equally satisfactory.

McKay²⁵ considers saline washings through the bronchoscope unsatisfactory. He and his associates have collected secretions on a cotton plug in the aspirator and have made their smears from this.

Every paper points out that Dudgeon and Wrigley,²⁶ in 1935, reported malignant cells in the sputum of 68 per cent of patients in a series of 38 cases with proved carcinoma of the lung. This work is quite obviously independent of that of Papanicolaou. It is most interesting to retrace the steps that led them to this study, for one finds it to be an adaptation of a technic reported by Dudgeon and Patrick²⁷ in 1927, in which scrapings of suspicious tissue from a variety of sources were spread on a slide and rapidly fixed, stained and examined. It appears that a pathologist, in his attempts at tumor diagnosis with smaller and smaller biopsies, has reached common ground with the cytologist.

UPPER GASTROINTESTINAL TRACT

The preparation of cellular spreads of gastric fluid must take into account certain factors not met in the secretion of the female genital and pulmonary tracts. Gastric fluid is less viscid, and the cells are much less numerous. Digestive ferments are present that will rapidly destroy the cells one wishes to study. Moreover, aspiration of stomach contents without roentgenologic check on the position of the tube runs the risk of failing to obtain a representative sample of the cells in the distal third of the stomach — an area where gastric carcinoma is most likely to occur.

Papanicolaou and Cooper²⁸ stress the importance of rapid fixation. They mix gastric fluid with an equal volume of 95 per cent alcohol, centrifuge for twenty minutes, spread the sediment on slides prepared with Mayer's albumen and then fix and stain them in their usual fashion. In a series of 27 cases of gastric cancer, positive smears were reported in 10 and suspicious ones in 7 others. There were no false-positive reports, but 9 of the 110 benign fluids were considered suspicious. Pollard and his associates,²⁹ using the same technic, found malignant cells in 35 to 40 per cent of patients with cancer of the stomach. They point out that satisfactory cytologic preparations are impossible in the presence of obstruction and gastric retention. This has also been emphasized by Ulfelder, Graham, and Meigs³⁰ who reported a high degree of accuracy (correct smears in 12 out of 14 patients with cancer of the stomach) when modifications in the method of collection were introduced. These include the use of a tube with additional openings in it and the introduction of physiological saline solution into the stomach in an effort to obtain a representative sample from the

entire organ. They stress the necessity of personal attention to the details of collection and preparation. Occasional false-positive smears were found by both Pollard and Ulfelder.

The malignant cells in gastric smears may be detected by application of the same criteria of abnormality postulated in the examination of other fluids. Most of the normal cells, however, are not gastric in origin, and familiarity with this normal picture is essential for accuracy.

URINARY TRACT

In dealing with urine one finds again that centrifugation is necessary to concentrate the cells in a small amount of sediment. Here also the use of albumen on the glass slides helps to retain the secretion during fixation and staining. Papanicolaou and Marshall³¹ add 95 per cent alcohol to freshly collected urine to retard cellular disintegration, although Chute and Williams³² discard this step in favor of immediate centrifugation and alcohol fixation of the sediment only.

Interpretation of urine smears is somewhat complicated by the lack of differentiation normally seen in transitional epithelium. Benign multinucleated cells are common. Moreover, many stages of activity are represented in any series of new growths of the urinary bladder, and a spectrum of grading is possible which crosses almost imperceptibly the line between benignancy and malignancy. Papanicolaou³³ reports 240 cases of which 76 are considered to have had carcinoma of the urinary tract. Fifty-eight (76 per cent) were diagnosed correctly by the smear. Three positive reports were rendered in the 164 patients considered not to have cancer, although 2 of them did have benign papillomas.

A much lower accuracy is reported by Chute and Williams. Only 55 per cent of cancers were detected, and there were 12 per cent false-positive reports. Most of the tumors missed were of low malignancy. Recently, Foot and Papanicolaou³⁴ reported a case of histologically proved noninvasive cancer of the renal pelvis invisible grossly but detected preoperatively by the cytologic method.

Both reports quoted in the paragraph above point out that carcinoma of the prostate may shed cells into the urine. Prostatic secretion collected by massage and immediately smeared, fixed and stained has been studied by Herbut and Lubin³⁵ and also by Albers and his co-workers³⁶. Both report an accuracy of over 85 per cent in cases of cancer if secretion is ample for smearing. A few positive smears that could not be confirmed histologically were also encountered.

SEROUS CAVITIES

Prior to the development of Papanicolaou's technique, more serious endeavor was applied to this type of fluid than to any other. A number of excellent reports³⁷⁻³⁸ are available, particularly since 1928.

The majority of pathologists centrifuge the fluid and fix and section the residue. The criteria used in diagnosis are dependable only when clusters of tumor cells in some recognizable architecture are present, although individual morphologic details have been carefully assessed and useful observations made on the nucleolar-nuclear ratio in benign and malignant cells.

A recent paper,³⁹ in which smears of sediment were used, reports an accuracy of only 56 per cent in cases in which cancer could be assumed to have involved the serous surfaces. This figure is no improvement over the 65 to 70 per cent accuracy reported in the past. There was, however, only 1 false-positive smear in this series whereas this type of error was common (25 to 50 per cent) in previous reports. One important deviation from Papanicolaou's technique should be noted in the procedure used by Phillips and McDonald³⁹: the smears were allowed to dry before fixation. In a series of 91 cases in which Papanicolaou's method was used without modification, the Vincent Memorial Laboratory⁴⁰ found malignant cells in 35 out of 45 cases. Four other positive smears were not corroborated histologically.

OTHER FLUIDS

The investigative curiosity of cytologists has extended to every conceivable material. It is known that rectal swabbings, duodenal aspirates, spinal fluid, ocular humors and many others are being examined. No formal reports have appeared, but it is probable that the fundamental technical principles are similar to those already described, with modifications to suit the character of each type of specimen.

DISCUSSION

It is obvious that exfoliative cytology can lead to the discovery of cancer in a variety of body areas, even when the lesion is invisible in size or histologically noninvasive. The results are most accurate when slides are prepared by a person interested in the procedure and willing to give time and attention to details that may facilitate interpretation, and when the slides are examined by someone thoroughly familiar with the cellular pattern of that particular fluid, prepared in that particular way.

Even under the best conditions available today there are two types of error—the false-negative and the false-positive cytologic report. The danger of the former is the unwarranted sense of security it gives to both patient and physician, it has analogies in any diagnostic procedure used in the cancer-detection clinic. This danger is so real that one must emphasize constantly the fact that failure to find cancer does not guarantee its nonexistence. It may be worth while in this connection to abandon any terminology of reporting that uses the words “negative,” “normal,” et cetera and to substitute phrases such as “no malignant cells found.”

The danger of the false-positive report is that radical therapy may be instituted with no attempt to find confirmatory evidence. Such patients should be subjected to frequent re-examination and managed according to a well planned study designed to determine exactly whence the abnormal cells arose. Serial section of any removed tissue is an essential feature of this program. As Gates and Warren point out, knowledge of the natural history of most malignant lesions is woefully meager in the early stages of disease. Now there is available a method that will permit more study of this type of case than has ever before been possible.

Looking at exfoliative cytology from quite another point of view, one may consider the chief disadvantage of the method to lie in its failure to *localize* the disease. For example, in a patient with malignant cells in the sputum and a small area of consolidation in one lung field, it is only the laws of probability that permit consideration of that area as the source of the cells. This will be true regardless of the eventual accuracy of the method and makes it essential that one discriminate very carefully in choosing between surgical procedures for confirmation and localization and surgical procedures for cure.

It may be best to think of the method as one that permits selection of some patients who are almost certain to have malignant lesions, for a repeatedly positive report from dependable sources is seldom wrong and warrants every possible effort at confirmation. By the same token, on the rare occasions when the malignant potential of a known tumor is in question, a positive smear should point the way to adequate cancer therapy.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35321

PRESENTATION OF CASE

First admission A twenty-nine-year-old married woman entered the hospital because of a nontender lump in her left breast.

She noticed this lump about six weeks before entry and it apparently had not increased in size since then. There had not been any bleeding from the nipple or soreness under the arm. The patient was nine and a half months post partum, having delivered a normal girl, her first child. She did not nurse the child because she did not believe she was emotionally suited to nursing. There was no weight loss or anorexia.

Except for the local lesion in the left breast, physical examination was entirely negative. The left breast was filled with a firm, grape-like cluster of nodules, densest in the inner middle quadrant. It was nontender, not fixed to the skin or chest wall and did not produce blood at the nipple on pressure. There was a bean-sized nodule in the left axilla.

A radial incision was made medial to the areola, and the involved area of breast tissue was excised. Immediate pathological examination showed no evidence of cancer, and the specimen received in the laboratory measured 5 by 4.2 cm and was diagnosed as sclerosing adenosis and periductal mastitis.

Second admission (ten months later) Soon after operation a small swelling developed near the operative incision, but this was considered to be an operative sequela. The patient received several doses of testosterone and then stilbestrol, with some improvement. However, because of the persistence of the mass and her continued anxiety, an aspiration was performed with return of old blood clot. It was believed that the lesion was a hematoma, and she was therefore admitted to the hospital for evacuation of it.

A circumareolar incision was made in the upper inner corner of the left breast. A considerable amount of blood clot was evacuated, together with a good deal of bright blood, and the incision was extended down along the line of the previous incision. The tissue was so necrotic and the bleeding so brisk that eventually a mastectomy was performed.

Third admission (four months later) After discharge the patient felt well and gained 6 pounds. About eight weeks before admission, however, she began to feel a slight pain in the upper outer quadrant of the right breast. She was examined by her physician seven weeks before entry, but no mass was palpable, however, the pain continued. One week before admission the patient was re-examined, and a mass was found in the right breast. She was therefore referred back to the hospital.

Physical examination showed an area of thickening, 2 by 3 cm, which was slightly firm, nontender and not well defined, in the upper, outer quadrant of the right breast. The scar of the left mastectomy was well healed.

On the second hospital day exploration of the right breast was performed.

DIFFERENTIAL DIAGNOSIS

DR GRANTLEY W. TAYLOR This is to my knowledge the briefest physical examination of a patient that I have ever seen in a clinicopathological conference. So this case will simply form some sort of text on which we can hang a number of not too brilliant diagnoses.

Here is a patient with something the matter with her breast, which was explored, who got into trouble postoperatively and in whom a mastectomy finally had to be done. I think that is deplorable. The findings on exploration—sclerosing adenosis and periductal mastitis—represent some of the disintegrated segments of the old category of chronic cystic mastitis. Foote and Stewart¹ subdivided that clinical group of diseases, and I noticed with a good deal of amusement that often one of the residents in pathology is apt to make seven or eight diagnoses in that category on a single patient. The problem of the relation of this disease to malignant neoplasm is one that is very poorly clarified. Dr. Shields Warren,² some years ago, undertook to find out what relation this general group of diseases called chronic cystic mastitis bears to the subsequent development of cancer. In reviewing patients who had had partial breast excisions or partial amputations that he had followed up he found that the incidence of cancer was definitely increased. The series was large enough to be statistically valid. Unfortunately, from my viewpoint, he did not subdivide the disease into the various subdivisions that Foote and Stewart recommend. Therefore, it is impossible to say which one of these various categories is the most likely

to be associated with subsequent development of the malignant process. He did divide the cases into age groups and found that if cystic disease had been manifested in the twenties, the likelihood of subsequent cancer was vastly greater than if the first evidence of disease did not appear until the forties or fifties. In the latter age group the incidence of subsequent cancer was almost identical with that of a control population.

We have a young woman who had such a diagnosis made in relation to her breast. It was removed, and she reappeared rather promptly with an area in the other breast. This had first put in its appearance as a painful area. Nothing is said in the record about whether the pain was related to the menstrual cycle in any way. I am inclined to believe that probably it was, because most cases of breast pain that do not have a mass associated with them are apt to manifest themselves in the week or ten days prior to the menstrual period, and then diminish considerably with the onset of the period. She was examined, and nothing was found in the breast. Presumably, a thorough search was made because she had symptoms directing attention to that area. It does not say whether the examining physician elicited any tenderness in that part of the breast, but it seems very likely since that was the area in which she complained of pain. However, the record says that during examination no mass was observed.

Now we come to the brief physical examination that described the mass, but descriptions of masses made by someone else are rarely satisfactory. I suppose nowhere is it more necessary to have one's own hand conduct an examination and then interpret the findings than in the examination of an ambiguous lump. It was well enough defined so that a guess about the measurements could be hazarded. She had an area of induration presumably in the same area where she had discomfort. The location in the outer upper quadrant is significant, since that is where patients more often have painful nodularity or the manifestation of sclerosing adenosis or cystic mastitis. That is the usual site, because that quadrant is the one that contains the largest amount of breast tissue. Nothing is said about the axilla, and we might assume that the axilla showed no metastases. That is as far as I can go on that. The rest is pure conjecture. All I can say is that we have, I think, very wisely adopted the attitude that every lump in the breast may be a cancer and that the only safe assumption is that it is a cancer until the pathologist says it is not. The general policy we have in relation to breast tumors in this hospital, and again I say it is a wise one, is that all such lumps are to be subject to exploration without undue delay. It used to be said that there is no good Indian but a dead Indian. We could modify this and say the only place for a lump in the breast is in a bottle

in the pathology laboratory. As long as a woman is harboring or may be harboring a cancer, immediate operation is warranted. Also, of the major cancers that affect mankind, cancer of the breast, if caught at an early stage, offers one of the most favorable prognoses of any type of malignant neoplasm. Therefore, if I were seeing this patient, I would say, "I cannot tell you what it is. It does not matter what I think it is. The important thing is that it is possible it may be cancer. Therefore, you should submit to exploration without delay and I will put it up to a pathologist. If it is not cancer, if it is benign, you will have the peace of mind that comes from the knowledge that it is benign. You will not be subjected to undue mutilation. [It would be harder to convince this patient on that point, because of the experience of the previous simple exploration with its unfortunate results.] You will be able to resume your usual activities in at least a week, if not sooner, and you will go on your way rejoicing that you do not have cancer."

If I were further pressed by this particular patient, or a member of the family, I would say "No, I do not think we are dealing with cancer in this case." Why? Because none of the positive evidence of cancer or the presumptive physical evidence was present. Here is a mass that had developed rapidly from being not observed at all to being 2 or 3 cm in size. It was first manifested by pain. There was no adherence and no distortion—only an area of induration described as an area of thickening. Again, one would want to feel it with one's own fingers to interpret it, but to me it is just a thickness that is not characteristic of cancer. In view of the fact that she had previously had sclerosing adenosis and mastitis in the opposite breast, I should think that this was a further manifestation of the same disease, which is of obscure etiology. Whether Dr. Nathanson will relate it to hormonal disturbances, whether it was of vascular origin or on what basis it originated, I am unable to say. But, I think it is going to be again the same thing that was found in the opposite breast.

DR. TRACY B. MALLORY: Dr. Bartlett, will you describe your findings?

DR. MARSHALL K. BARTLETT: Naturally, it was very distressing to have this patient come back after operation with a residual mass in her breast. Because we had a pathological report of a benign lesion, it seemed safe to experiment a little with hormonal therapy, but it failed to produce any significant change in the lesion. During this period the patient and her family were not happy about the situation and presently sought the opinion of another surgeon. He observed it for a time and then finding a bluish discoloration of the skin, he aspirated it, and got some blood out of it that led him to the conclusion that probably it was an old

hematoma, and as related in the record, she was admitted for evacuation of the hematoma. At that time, the bleeding encountered was so massive that operation was limited to biopsy of the tissue. As a result of the report of that biopsy, the patient was seen by several consultants and, on their advice, I finally did a radical mastectomy on her. Her convalescence was uneventful, and she was well for several months, as you have been told. She finally came back complaining of the other breast in which I could find no lesion, but for obvious reasons I suggested re-examination in a few weeks. At that time there was a mass. This mass was then excised, and immediate pathological examination made. There was no evidence of carcinoma. However, when the final sections came through an opinion was expressed that led to a radical mastectomy on the opposite side.

CLINICAL DIAGNOSIS

Chronic cystic mastitis

DR TAYLOR'S DIAGNOSES

Sclerosing adenosis of breast
Periductal mastitis

ANATOMICAL DIAGNOSIS

Hemangiosarcoma of breast

PATHOLOGICAL DISCUSSION

DR MALLORY: This case represents complete failure on the part of the Department of Pathology, and of me personally, to detect a malignant lesion of the breast. When Dr Bartlett explored the first lesion in the left breast, I was present at the operation, and the tissue seemed so obviously benign that I did not consider it necessary to do a frozen section. We then put through a paraffin section and did find, as reported, adenosis.

At the time of the recurrence and the second biopsy, it became obvious that there was a malignant tumor, of endothelial origin, present in the breast.

DR JOSEPH C AUB: Which breast?

DR MALLORY: The left breast. It was a hemangioma growing with rapidity, so that we had to classify it as a hemangiosarcoma. At that time the radical mastectomy was done. The subsequent recurrence in the second breast was identical. Again, the biopsy looked perfectly benign grossly but on microscopical examination had the same type of malignant vascular tumor in it. When the recurrence appeared in the first breast, we went back to the original biopsy and found in one corner of one of our slides a little area, which had we paid attention to it, we should have recognized certainly as a hemangioma, if not as a malignant one.

DR RICHARD H WALLACE: Was the axilla involved on either side?

DR MALLORY: No, there was considerable question on both occasions whether or not radical mastectomy should be done. Very often these hemangiomas do invade the pectoral muscles. It was believed that if one was going to remove the pectoral muscles it did not add much to the operation to dissect the axilla.

Have you any comment, Dr Taylor?

DR TAYLOR: No, except that I am pleased to take a nose dive in such good company.

A PHYSICIAN: How long has it been since operation?

DR BARTLETT: About a year. The patient is all right at the present time.

DR TAYLOR: Was the second tumor an independent primary tumor or a metastasis?

DR MALLORY: I believe it was independent. It was in the other breast, and on the far side. If the recurrence had been close to the line of the original incision, one would think otherwise.

DR IRA T NATHANSON: I saw this patient with Dr Bartlett. The lesion in the right breast was a ring for sclerosing or blunt duct adenosis. We could not make a diagnosis of hemangiosarcoma although we entertained it in view of the findings in the left breast. Consequently, we decided to explore the area in order to establish the diagnosis.

The various types of sarcomas of the breast rarely metastasize to lymph nodes but usually spread through the blood stream, commonly to the lungs. Hence, simple mastectomy has been ordinarily considered adequate to control the local disease. However, sarcomas of the breast, particularly of hemangiomatous origin, may invade the pectoral muscles. This was seen on the left side, where radical mastectomy was performed for this type of invasion. Similarly, it was our opinion that radical mastectomy on the right side was also the procedure of choice in this patient, who was in excellent physical condition. It was considered that the slight additional risk was minor in comparison with the possibility of leaving residual disease in the muscle if simple mastectomy was elected.

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CASE 35322

PRESENTATION OF CASE

A twenty-four-year-old married woman entered the hospital because of morning hemoptysis.

The patient had been well until shortly after a pregnancy and delivery under ether anesthesia eight months before admission, when she developed a chronic cough, particularly in the morning, productive of a tablespoonful of whitish-yellow, non-

foul sputum. This persisted and in the three months before entry became associated with a dull, aching and occasionally sharp twinge of right subscapular pain on coughing. The patient denied chills, fever, night sweats and other constitutional symptoms, but noted progressive fatigability and a 15-pound weight loss despite a good appetite. The fingernails seemed to change during this period from normal configuration to a clubbed appearance. Three weeks before entry the patient had the onset of morning hemoptysis from a teaspoonful of bright-red blood to bloody streaking of the sputum. This was a daily occurrence but was unassociated with new symptoms or change in other symptoms. Five years before admission the patient developed a firm, nontender, and otherwise asymptomatic mass in the right anterior cervical region, which was removed in another hospital and allegedly found to contain a "pocket of pus." About two years before admission she noted the gradual recurrence of a mass in the same region, with some increase in size up to the present.

The family and past histories were not remarkable. The patient denied known contact with tuberculosis.

Physical examination revealed a slender, well developed woman in no discomfort. There were several firm, nontender, freely movable, nodular masses in the right anterior cervical triangle—one measuring 2 by 3 cm, with adjacent 0.5-cm nodules on the sternomastoid muscle, and one measuring 2 by 5 cm in the supraclavicular fossa, which seemed to descend into the upper mediastinum. No other significant lymphadenopathy or abnormal masses were noted except for a slightly tender, freely movable mass, 2 by 5 cm, in the right breast and a similar mass, 2 by 3 cm, in the left breast. Early clubbing was noted in all fingernails. Examination of the chest revealed signs consistent with consolidation in the right upper lobe, most marked anteriorly. There were a Grade I short, blowing, basal systolic murmur and a split second sound at the base. The remainder of the physical examination was not remarkable.

The temperature was 98.6°F, the pulse 100, and the respirations 20. The blood pressure was 125 systolic, 70 diastolic.

Examination of the blood disclosed a white-cell count of 14,000, with 92 per cent neutrophils. The hemoglobin was 11 gm per 100 cc. Urinalysis revealed a + test for albumin and was otherwise negative. Sputum examination for acid-fast bacilli was negative. A skin tuberculin test was negative in dilutions of 1:100,000 and 1:10,000.

X-ray study of the chest revealed increased density in the anterior segment of the right upper lobe, with some degree of collapse and honeycombing in the lower portion of the lobe, interpreted as dilated bronchi. There was increased prominence of the right hilus, and some calcification was demonstrated in the right lung. The left lung was normal.

The findings were interpreted as "drowned" lung, secondary to obstruction in the right-main-stem bronchus.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR JOHN G. SCANNELL. In second-year medical school we were asked in an examination to enumerate and discuss the causes of hemoptysis and were expected to rattle off with a fair degree of assurance the fourteen (or was it seventeen?) diseases concerned. I wish I could muster the same assurance today. However, assuming that the hemoptysis was bona fide, and in the present case there is every reason to believe that it was, we must look to the bronchial tree for either a primary lesion or changes secondary to pulmonary hypertension. With no evidence for the latter, I think we can safely dismiss it and confine our attention to diseases that give rise to localized changes in the lungs, to a definite lymphadenopathy and to generalized systemic changes—namely, weight loss, chronic fatigue and clubbing. As a point of departure, may we see the x-ray films?

DR JAMES C. MCCORT. The examination of the chest reveals an increase in density of the anterior and apical segments of the right upper lobe. These segments are reduced in size. Within the involved segments there are radiolucent areas giving the segments a honeycombed appearance. This may be due to dilated bronchi and bronchioles. None of these radiolucent areas show a fluid level. There is a slight amount of fluid in the overlying pleura and in the minor fissure on the right side. The right-upper-lobe bronchus can be traced for a distance of 1 cm distal to its orifice, at which point it is narrowed and apparently blocked. There is no definite evidence of displacement of the trachea or mediastinum. Enlargement of the right peribronchial lymph nodes is present. There are also a few flecks of calcification in the peribronchial area, which may be within lymph nodes. The remaining lung fields are clear. The diaphragm is in its normal position. There is no blunting of either costophrenic sinus. The heart and vessels appear normal.

DR SCANNELL. Are you impressed by the curving deviation of the trachea to the left? I assume that is compatible with the large lymph node in the right cervical triangle described in the physical examination.

DR MCCORT. The cervical portion of the trachea does show a slight displacement to the left side, which may be due to the mass described in the right side of the neck. The exact amount of displacement is difficult to determine because there is slight scoliosis of the spine.

DR SCANNELL. We have, therefore, evidence of a lesion that involved bronchi of the order of

segmental bronchi, and hence presumably could be visualized and, perhaps, biopsied through a bronchoscope. There were also cervical lymph nodes that, according to the description given, were sufficiently abnormal to warrant biopsy. We are, however, called upon to make a diagnosis in advance of these diagnostic maneuvers.

In a patient of another sex and another age group, the diagnosis would be carcinoma until proved otherwise. The marked male-sex preference of bronchiogenic carcinoma is well known (usually estimated to be about ten to one), and in a patient in the twenties the unlikelihood of carcinoma is greatly increased. Except for these facts, however, the history of an unfamiliar cough, dull, aching chest pain, weight loss, chronic fatigue and, especially, early pulmonary osteoarthropathy are all highly suggestive, and the finding of a segmental lesion by x-ray examination and enlarged cervical, paratracheal and mediastinal lymph nodes is almost confirmatory. To rule out cancer requires a positive diagnosis of something else, presumably benign tumor, a chronic suppurative process or tuberculosis.

We might mention other rare tumors, notably chorionepithelioma and lymphoma. The former is, perhaps, suggested by the onset following pregnancy, but that is all that we have in its favor and I shall discard it. Lymphoma of the lung is rare, particularly with endobronchial involvement, but it is known to occur, it may invade the bronchial tree, and certainly is suggested here in view of the rather striking cervical-lymph-node involvement and the evidence of considerable hilar lymphadenopathy by x-ray examination. In addition, we have the evidence of a chronic disease without great blood loss. I am a little disturbed by the apparent lack of fever.

In the case of lymphoma of the lung reported from this hospital by Dr Churchill¹ in 1947, there were several points of similarity to the present case. The patient was a woman, she complained of a dull aching pain beneath the right scapula, and her physical signs were those of consolidation—that is, an open lobar bronchus with solidified lung adjacent to it. On the other hand, she had no lymph-node involvement, no clubbing, no hemoptysis and no anemia. She had had symptoms some six months or so, with episodes of fever. However, the case presented apparently a solitary lymphoma of the lung itself, and not, as we must postulate in the case under discussion, a lymphoma situated in the right bronchial node and invading and involving the right-upper-lobe bronchi secondarily. Certainly, the cervical lymph nodes suggest lymphoma in that they were freely movable, firm, nontender and of considerable size. Were they of tuberculous origin I would expect them to be less discrete, more uniformly involved and possibly displaying some calcification on x-ray study. Furthermore, a def-

inite diagnosis of tuberculosis was ruled out by negative sputums and negative tuberculin tests. An acid-fast node eroding into a bronchus is, in a way, an attractive diagnosis to make for this patient, but I do not see how we can support it.

Of the possibilities outlined above, benign tumor was mentioned. The patient was a woman, she was young, she had had some bleeding, and she had segmental secondary changes. However, this diagnosis fails to account for the enlarged lymph nodes, except the very rare bronchial adenoma with extensive satellite-lymph-node involvement. In any case, were the latter involved secondary to a pulmonary lesion, I would expect greater involvement of the subcarinal node, and as we can see by the overexposed film of the chest, the carina is quite sharp and normal in appearance. Incidentally, were the lesion a highly undifferentiated bronchiogenic carcinoma of the oat-cell variety, I should expect the same distortion of the carina as is present in this case.

Turning to a more hopeful diagnosis, in view of the onset of cough following an inhalation anesthesia, chronic lung abscess must be carefully considered. Chronic, somewhat productive cough, hemoptysis and clubbing are in its favor. Absence of fever, the presence of cervical lymph nodes and the location in the anterior and apical segments of the upper lobe as opposed to the posterior segment of that same lobe are against it. Both by history and on x-ray study there was no evidence of a sequestration of lung tissue. Furthermore, no penicillin or streptomycin had been given, which might obscure the natural history of the disease.

Bronchiectasis limited to the right upper lobe is a possibility, but here again the history is relatively short and atypical, the x-ray picture, in spite of the suggestion of dilated bronchi, is not that of saccular, dry bronchiectasis in this area, and the cervical lymph nodes are not accounted for. Bronchiectasis secondary to a foreign body is always a possibility, especially in view of the previous anesthesia, but we have no evidence on which to base this diagnosis.

A closely related lesion—namely, chronic non-specific pneumonitis of the cholesterol type²—certainly merits our consideration. The history is not at all out of line, although one would expect more evidence of an active inflammatory process at some time in its development and less striking hemoptysis, and although marked regional lymphatic involvement is the rule (and is evident here on the chest film), again the presence of these definitely abnormal cervical lymph nodes is difficult to explain. Strangely enough, at no time was viral pneumonia diagnosed and antibiotics given.

One always wonders, particularly in this hospital, about the diagnosis of sarcoid in puzzling lymphatic and pulmonary lesions, but if I understand Dr Freiman³ aright, even considerable enlargement

foul sputum This persisted and in the three months before entry became associated with a dull, aching and occasionally sharp twinge of right subscapular pain on coughing The patient denied chills, fever, night sweats and other constitutional symptoms, but noted progressive fatigability and a 15-pound weight loss despite a good appetite The fingernails seemed to change during this period from normal configuration to a clubbed appearance Three weeks before entry the patient had the onset of morning hemoptysis from a teaspoonful of bright-red blood to bloody streaking of the sputum This was a daily occurrence but was unassociated with new symptoms or change in other symptoms Five years before admission the patient developed a firm, nontender, and otherwise asymptomatic mass in the right anterior cervical region, which was removed in another hospital and allegedly found to contain a "pocket of pus" About two years before admission she noted the gradual recurrence of a mass in the same region, with some increase in size up to the present

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In a patient of another sex and another age group, the diagnosis would be carcinoma until proved otherwise. The marked male-sex preference of bronchiogenic carcinoma is well known (usually estimated to be about ten to one), and in a patient in the twenties the unlikelihood of carcinoma is greatly increased. Except for these facts, however, the history of an unfamiliar cough, dull, aching chest pain, weight loss, chronic fatigue and, especially, early pulmonary osteoarthropathy are all highly suggestive, and the finding of a segmental lesion by x-ray examination and enlarged cervical, paratracheal and mediastinal lymph nodes is almost confirmatory. To rule out cancer requires a positive diagnosis of something else, presumably benign tumor, a chronic suppurative process or tuberculosis.

We might mention other rare tumors, notably chorionepithelioma and lymphoma. The former is, perhaps, suggested by the onset following pregnancy, but that is all that we have in its favor and I shall discard it. Lymphoma of the lung is rare, particularly with endobronchial involvement, but it is known to occur, it may invade the bronchial tree, and certainly is suggested here in view of the rather striking cervical-lymph-node involvement and the evidence of considerable hilar lymphadenopathy by x-ray examination. In addition, we have the evidence of a chronic disease without great blood loss. I am a little disturbed by the apparent lack of fever.

In the case of lymphoma of the lung reported from this hospital by Dr Churchill¹ in 1947, there were several points of similarity to the present case. The patient was a woman, she complained of a dull aching pain beneath the right scapula, and her physical signs were those of consolidation—that is, an open lobar bronchus with solidified lung adjacent to it. On the other hand, she had no lymph-node involvement, no clubbing, no hemoptysis and no anemia. She had had symptoms some six months or so, with episodes of fever. However, the case presented apparently a solitary lymphoma of the lung itself, and not, as we must postulate in the case under discussion, a lymphoma situated in the right bronchial node and invading and involving the right-upper-lobe bronchi secondarily. Certainly, the cervical lymph nodes suggest lymphoma in that they were freely movable, firm, nontender and of considerable size. Were they of tuberculous origin, I would expect them to be less discrete, more uniformly involved and possibly displaying some calcification on x-ray study. Furthermore, a def-

inite diagnosis of tuberculosis was ruled out by negative sputums and negative tuberculin tests. An acid-fast node eroding into a bronchus is, in a way, an attractive diagnosis to make for this patient, but I do not see how we can support it.

Of the possibilities outlined above, benign tumor was mentioned. The patient was a woman, she was young, she had had some bleeding, and she had segmental secondary changes. However, this diagnosis fails to account for the enlarged lymph nodes, except the very rare bronchial adenoma with extensive satellite-lymph-node involvement. In any case, were the latter involved secondary to a pulmonary lesion, I would expect greater involvement of the subcarinal node, and as we can see by the overexposed film of the chest, the carina is quite sharp and normal in appearance. Incidentally, were the lesion a highly undifferentiated bronchiogenic carcinoma of the oat-cell variety, I should expect the same distortion of the carina as is present in this case.

Turning to a more hopeful diagnosis, in view of the onset of cough following an inhalation anesthesia, chronic lung abscess must be carefully considered. Chronic, somewhat productive cough, hemoptysis and clubbing are in its favor. Absence of fever, the presence of cervical lymph nodes and the location in the anterior and apical segments of the upper lobe as opposed to the posterior segment of that same lobe are against it. Both by history and on x-ray study there was no evidence of a sequestration of lung tissue. Furthermore, no penicillin or streptomycin had been given, which might obscure the natural history of the disease.

Bronchiectasis limited to the right upper lobe is a possibility, but here again the history is relatively short and atypical, the x-ray picture, in spite of the suggestion of dilated bronchi, is not that of saccular, dry bronchiectasis in this area, and the cervical lymph nodes are not accounted for. Bronchiectasis secondary to a foreign body is always a possibility, especially in view of the previous anesthesia, but we have no evidence on which to base this diagnosis.

A closely related lesion—namely, chronic non-specific pneumonitis of the cholesterol type²—certainly merits our consideration. The history is not at all out of line, although one would expect more evidence of an active inflammatory process at some time in its development and less striking hemoptysis, and although marked regional lymphatic involvement is the rule (and is evident here on the chest film), again the presence of these definitely abnormal cervical lymph nodes is difficult to explain. Strangely enough, at no time was viral pneumonia diagnosed and antibiotics given.

One always wonders, particularly in this hospital, about the diagnosis of sarcoid in puzzling lymphatic and pulmonary lesions, but if I understand Dr Freiman³ aright, even considerable enlargement

of the hilar lymph nodes is rarely associated with pressure or obstructive phenomena, a point of differentiation from lymphoma or carcinoma

Metastatic carcinoma is also a definite possibility, and in this case would incriminate the thyroid gland or some silent primary focus. We have little evidence to single out the former, and no real evidence to indicate the latter — for example, a silent hypernephroma. At some risk, I am going to disregard the bilateral breast masses

Clearly, a most helpful next step in the diagnosis would be either a bronchoscopic biopsy or a cervical-lymph-node biopsy, and one of these, I suspect, was the operation performed on the fourth hospital day. When I embarked upon this discussion, I was inclined toward a nonspecific chronic pneumonitis with marked hilar involvement, believing that the history, the age and sex of the patient, the x-ray picture and the physical signs were consistent with this diagnosis, but as I reconsider it, I am more than ever impressed by the cervical lymphadenopathy and therefore elect lymphoma with bronchial encroachment and erosion as the probable diagnosis

CLINICAL DIAGNOSIS

Malignant lymphoma

DR SCANNELL'S DIAGNOSIS

Malignant lymphoma

ANATOMICAL DIAGNOSIS

Malignant lymphoma, Hodgkin's type

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN On the ward, the differential diagnosis rested mainly between tuberculosis and lymphoma. Dr Joseph C. Aub, who was on service at that time, believed that "the most

reasonable single diagnosis is lymphoma occluding the bronchus"

One of the cervical lymph nodes was removed, and it showed the characteristic microscopical findings of Hodgkin's disease. Dr Benedict reported that bronchoscopy of the right bronchial tree was difficult because of the apparent pressure on it from the right side, but with the right-angle telescope, the orifice of the upper lobe was readily visible and found to be markedly stenotic. No outcropping could be seen.

The patient was then given x-ray treatment over a period of eight days, 300 r per day, the anterior and posterior right upper mediastinum each receiving 900 r and the supraclavicular region 600 r.

The patient did not return to this hospital, but it was later learned that there was a good response to this treatment for about a year. She then entered another hospital very sick with fever, weight loss, anemia, pleural effusion and ascites. After tapping of the chest, a mass was observed within the right lung and after tapping of the abdomen, the liver and spleen were found to be enlarged. X-ray treatment was again given, but this time there was no improvement. However, a course of nitrogen mustard produced a miraculous change in the patient. The mass in the lung practically disappeared, and the patient was able to be herself again. This remission lasted for about three weeks, but she then returned with pain in the opposite chest. Nitrogen mustard again brought relief. She has just recently been discharged from the hospital after her third remission, which is about two years since admission to this hospital.

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EDUCATION OF THE FAMILY PHYSICIAN

OF ALL the manifold problems besetting the medical profession today in its desire to provide the public with the best medical care, that of restoring the family physician to a position commensurate with his contribution to society, by improving standards of general practice, appears to be one of the most pressing

The pattern of practice is obviously changing, and the next few years will undoubtedly bring profound alterations in the organization for the provision and distribution of medical care, as well as in the methods of paying for it. Nevertheless, there can be no change in what is fundamental to the best medical practice—namely, a solid foundation of well trained family physicians. True, the public has strayed away from reliance on the family doctor owing largely to overemphasis of

specialization, so highly developed and widely touted in all phases of American life, but there seems now to be a trend back to him, with a beginning awareness of the proper relation between the general physician, as the first echelon, and the specialist, whom he will call when needed. Not the least of the influences in this change may be certain types of group practice in which several general practitioners or family physicians work on an equal footing with various specialists to whom they refer patients as indicated. Regardless of whether group medicine is to become the accepted pattern and whether prepayment insurance becomes the solution for the economic difficulties, nothing will succeed in replacing the family physician as the most important cog in the whole system.

Actually, the profession itself is largely responsible for the devaluation of the family doctor. Clinical teaching in the medical schools is largely provided by specialists, and postgraduate education of interns and residents in teaching hospitals is chiefly carried out by specialists and research workers. The house staff tends to believe that going into practice is a less worthy career than one devoted to teaching and research—a step downward, rather than merely a parallel road. The family physician who refers problem cases to these hospitals is often looked down upon by the house staff, and referred to patronizingly as the "L M D." Perhaps teaching hospitals should arrange for qualified general practitioners to enter into certain phases of teaching. The family doctor is likewise to blame by trying to do too much and becoming so busy he cannot keep up with attendance at meetings or with the medical literature. Instead he would do well to put such educational activities on a required list each week. Too often he has had insufficient hospital training, and the opportunities for good training for this type of work are too few and poorly organized.

The economics of medicine adds to the process of his devaluation. Although he must combine the skills of diagnostician, therapist for at least 75 per cent of the problems confronting him, adviser for family and individual social problems, and public-health adviser, for all these diffuse but vital functions he is undercompensated in comparison with many specialists.

Finally, there appears little doubt that the process of board certification has gone too far, par-

ticularly in internal medicine. Certainly, a great many certified "internists" are, actually, family physicians. Yet the prize of a certificate by the Board of Internal Medicine is such that men planning to devote themselves to medicine rather than to surgery or other specialties requiring technical skills are often motivated in planning their hospital training by getting so many years of credit—putting in time, so to speak—rather than by an intrinsic desire for postgraduate study per se. Too little consideration is given to the fact that medical education is a lifelong process, and even though a man goes into practice he must continue to develop himself educationally in the wards and at conferences of the hospital of his community. Although two years of internship training should be a minimum for the family physician it might be very desirable to revive the old apprentice system whereby the young physician works for a year under the supervision of an older staff member of a community hospital. If this could be effectively carried out, it would probably be more valuable than an additional hospital residency.

Recently the Council on Medical Education and Hospitals of the American Medical Association has included a residency in general practice in its "Essentials of Approved Residencies and Fellowships." This residency is designed to attract men who wish to become family physicians, and is not conceived with the thought that specialty boards will accept it as meeting in part their training requirements. This and other movements are in line with the trend toward elevating standards of general practice as required by modern life, and in elevating the position of the modern family physician. In Boston the Faulkner Hospital has announced a new internship of two years, designed to provide optimum training in this field. Emphasis is placed on internal medicine, to which twelve months are devoted, with another year divided among pediatrics, obstetrics and surgery. A period devoted to medicine and pediatrics is to be spent at a larger teaching hospital in affiliation. The internship is announced as being especially designed for men who wish to become family physicians.

Such programs should go far toward improving the level of general practice and should result in attracting more and better men into this field. Perhaps one of the most important factors in combating the demand for compulsory health insurance

will be the development of many well trained family physicians, with a better sense of proportion, both within the profession and on the part of the public, concerning specialization.

"WHAT IS A MAN PROFITED?"

HOFFMAN, elsewhere in this issue of the *Journal*, considers the clinical results of leukotomy in 42 patients treated by psychosurgery at the Veterans Administration Hospital in Bedford, Massachusetts. The study covers the years 1947 and 1948. All but one of the patients were schizophrenics whose illness and hospitalization had been of two to twenty years' duration. Results at the time of the study showed 4 patients to be dead, 14 out of the hospital, either discharged or on trial visits, 16 still in the hospital but so improved that they could have been living at home, and 8 still in the hospital and requiring hospital care because of continued disturbed behavior.

These results are comparable to those more recently released by the Yale University News Bureau on the Connecticut Co-operative Lobotomy Study, a joint project of the Department of Psychiatry and Mental Hygiene of the Yale University School of Medicine and the three state mental hospitals of Connecticut. This study, organized in 1946, reports on 294 postoperative patients, mostly severe cases of schizophrenia, who had been hospitalized for an average of five years prior to operation.

According to this report 36 per cent of the patients were able to return to their homes within a year after operation, and a total of 61 per cent had shown definite improvement in their mental health. An important measure of their status is their capacity for work. Of the 294 patients less than 75 per cent were capable of work before their operation. After the lobotomy more than 25 per cent were working full time, and an additional 38 per cent were employed on a part-time basis.

So far as objective behavior is concerned, impulsive, overactive and aggressive traits, suicidal attempts and constant refusal of food had disappeared in over three fourths of the group. Subjectively, more than 85 per cent of the patients had lost such disturbing symptoms as depression, obsessive-compulsive behavior and anxiety.

These figures are certainly encouragingly in favor of the operation, but Hoffman presents also the

other side of the argument, considering his cases from the point of view of qualitative results. The behavior and frequently the comfort of the patients is admittedly improved, but it is by the process of subtraction, he implies, and never by addition.

The tendency, he points out, is to overlook "the very real and permanent losses to the integrity of the personality" sustained as a result of operation. In the removal of the disease focus an uncertain quantity of vital tissue indispensable in making up the total personality of the patient is also removed. Even in consideration of a certain general vagueness concerning just what constitutes a soul, some observers have described post-lobotomy patients as persons who had lost this ill defined but apparently indispensable part of their individuality. Perhaps it would be more acceptable to say that many of them had lost the vital spark of their personality, or the particular spiritual value compounded of the emotions and the reason, and consisting of the ability to know sorrow and happiness, peace and anxiety, compassion and understanding that puts the final touches on the human being.

Psychosurgery is one of the fruitful experiments that medical science has occasionally to offer, but its subjects must still be selected with the utmost care. Perhaps, as Greenblatt and Myerson* suggest, the refinements of topectomy will avoid some of the disadvantages of lobotomy.

*Greenblatt M and Myers P G. Psychosurgery. *New Eng J Med* 240 1006-1017 1949

SOLOMON'S KITCHEN

KING SOLOMON, it is said, on a visit to Hebron, found the people of the district so poor and yet so loyal that he established a fund to provide them with daily food "until the end of the world." Presumably Solomon's fund has been exhausted, but so strong is tradition that the custom has been maintained even to the present time.

Last December, however, the continuity of the practice established by the wise king was at last about to be broken. The cupboard was bare. Then on Christmas eve trucks of the United Nations International Children's Emergency Fund rolled into the area.

A million refugees, *UNICEF News* reports, are waiting out their destiny in the desert about Israel. Food and shelter are their first problem, idleness

comes next. Schools have been started for the children, but there are no fields for the men to till, no wool for the women to weave. UNICEF is now able to bring some measure of relief to the half million children and pregnant and nursing women among these refugees—a relief, purchased out of the allocation of \$6,411,000 made to the area by the executive board, that comes from all over the world.

The United States, Canada and Denmark have sent milk, cod-liver oil has come from Iceland, and margarine from Australia and Belgium. Meat, wheat and flour have come also from Australia, and wheat and flour from Ethiopia, dried fruit has been sent from South Africa and Yugoslavia, rice from the Dominican Republic, Italy and Siam, and soap from New Zealand.

Palcstine is but one of the areas where the world's present misery makes such aid as that furnished by UNICEF imperative. In the first year of the program's operation 84,000,000 supplementary meals were provided in Austria. Shoes and blankets are now being distributed in Bulgaria. Czechoslovakia, a donor as well as a recipient country, has received over \$3,000,000 in supplies, with the government contributing \$1,000,000 and the people having raised an additional \$300,000.

In Greece 670,000 children and women, of whom 250,000 are refugees, receive supplementary meals, over a million Italian children are fed daily. Meals are provided in Yugoslavia, a BCG antituberculosis vaccination program is under way in Morocco, health workers are being trained in China. Danish teams of BCG vaccinators are at work in India, and a UNICEF Medical Mission is operating in Pakistan. Children are being fed in the Philippines.

The small countries, it is interesting to note, are leading in the response to the United Nations appeal for children, and of these Iceland, with a per capita contribution of \$4, leads all the rest. Other material donations have come from Australia, New Zealand, South Africa, Canada, Mozambique. Czechoslovakia raised a total of \$1,500,000, \$300,000 of which was for UNICEF. Yugoslavia and Austria have made their contribution, and even Italy has raised a quarter of a million dollars.

If the strength of a nation, as has been written, lies in the hearts of its people, then the world may yet struggle through its present misery to a better way of life.

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JOSEPH T WALKER, PH D

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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PHYSICIANS' HANDBOOK ON BIRTH AND DEATH REGISTRATION

The Massachusetts Department of Public Health has arranged with Edward J Cronin, secretary of the Commonwealth, to send copies of the tenth edition of the *Physicians' Handbook on Birth and Death Registration* to all practicing physicians and boards of health in Massachusetts. This handbook is valuable to physicians because it gives the important facts that physicians should know regarding registration requirements and procedures.

Additional copies can be obtained by application to the Secretary of State's office, State House, Boston 33, Massachusetts.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Research Publications Association for Research in Nervous and Mental Disease. Volume XXVII. *The Frontal Lobes. Proceedings of the Association, December 12 and 13, 1947*. New York 8°, cloth, 901 pp, with 237 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$12.50.

Fifteen years ago the Association published its volume on the localization of function in the cerebral cortex. The present volume deals with the frontal lobes and the material is divided into four parts: biology, experimental studies, clinical studies and frontal lobotomy. There are twenty-seven articles in this volume of the Research Publications, twenty-one of which are now out of print and unobtainable from the publishers or the Association. The series is very valuable and should be in all medical libraries. The present volume should be available to all neurologists and psychiatrists.

Industrial Hygiene and Toxicology. Volume I. Frank A Patty, editor. 8°, cloth, 531 pp, with illustrations and tables. New York: Interscience Publishers, Incorporated, 1948. \$10.00.

This volume is the first of a set of two projected volumes. Eleven specialists have contributed to this part, which is devoted to the various aspects of industrial hygiene. Some of the topics include personal and environmental factors in fatigue and competence, physiologic effects of abnormal atmospheric pressure, the mode of entry and action of toxic materials, sampling and analysis of atmospheric contaminants, radiant energy and radium (including poisoning by radium and thorium), ventilation, occupational dermatoses, the visible marks of occupation and occupational diseases, fire and explosion hazards of combustible gases, vapors and dusts, respirators and respiratory protective devices and dust and its role in occupational diseases. The literature noted is printed as footnotes on the pertinent pages. There is an extensive index of subjects. The type, printing and paper are excellent. Although this volume is large, it weighs only 3 pounds. Volume II, to be published later, will be devoted to various toxic compounds. The set is recommended for all medical public-health and industrial-plant libraries.

NOTICES

ANNOUNCEMENT

Dr Elmore M Campbell announces the opening of an office for the practice of medicine at 187 East Cottage Street, Dorchester.

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The National Gastroenterological Association will hold its fourteenth scientific session at the Hotel Somerset in Boston, on October 24-26, 1949.

Among the outstanding speakers to present papers at the convention will be Dr Owen H Wangersteen, professor of surgery, University of Minnesota Medical School, Dr Frank H Lahey, Dr William B Castle, and Dr Maxwell Finland, of Boston, Dr George Crile, Jr, Cleveland, Ohio, Dr J M T Finney, Jr, Baltimore, Maryland, and Lord Alfred Webb-Johnson, president of the Royal College of Surgeons, London, England, who will be a guest of honor at the banquet to be held on Tuesday evening, October 25.

At the annual banquet to be held at the Somerset, the winner of the National Gastroenterological Association's 1949 prize award contest for the best unpublished contribution on gastroenterology or an allied subject, will receive the prize of \$100 and a certificate of merit.

Immediately following the convention on October 27-29, 1949, the Association is sponsoring a course in gastrointestinal surgery at the Boston City Hospital.

Further information concerning the program and details of the course may be obtained by writing to the secretary, National Gastroenterological Association, 1819 Broadway, New York 23, N Y.

AMERICAN PUBLIC HEALTH ASSOCIATION

The annual meeting of the American Public Health Association and related organizations will be held in New York City from October 24 to 28, with joint headquarters at the Hotel Statler and Hotel New Yorker. At the two general sessions of the Association the Lasker Awards for 1949 and the Sedgwick Memorial Medal will be presented, and the address of the president, Dr Charles F Wilinskas, of Boston, will be read.

Details regarding the program may be obtained from Dr Reginald M Atwater, Executive Secretary, American Public Health Association, 1790 Broadway, New York City.

AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics will hold its annual meeting in San Francisco, California, at the Palace Hotel, November 14 to 17, 1949.

PAN-AMERICAN CONGRESS OF PEDIATRICS

The second Pan-American Congress of Pediatrics (Tenth District of American Academy of Pediatrics) will be held in Mexico City, at the Del Prado Hotel, from November 2 to 5. The third National Congress of Pediatrics of the Mexican Society of Pediatrics will be held in Mexico City from October 30 to November 10.

INTERNATIONAL COLLEGE OF SURGEONS

The annual assembly and convocation of the International College of Surgeons, United States Chapter, will be held in Convention Hall, Atlantic City, from November 7 to 12.

The program will include scientific sessions on general surgery, eye, ear, nose and throat surgery, gynecology and obstetrics, urology, and orthopedic, thoracic, plastic and neurologic surgery. Special surgical clinics will be held in Philadelphia hospitals on November 7.

All doctors of medicine interested in surgery are invited. Further information regarding the program may be obtained from Dr Arnold S Jackson, secretary of the Chapter, at the Jackson Clinic Madison 4, Wisconsin. Hotel reservations may be made with E D Parrish, Haddon Hall, Atlantic City, New Jersey.

Such shocking exhibitions of dyed heads as are occasionally met with in the streets, in this change loving age, when fashionable people think they can color their skins and their hair with as much ease as politicians turn their coats under a new administration, show the necessity of a more perfect and expeditious mode of accomplishing the metamorphosis

Boston M & S J, August 8, 1849

NOTES FROM THE MEDICAL EXAMINER

IDENTIFICATION OF BLOODSTAINS — II

The proof that a stain has been caused by blood is a significant step in its identification¹ To show that it has been caused by human blood is of much greater importance

Before the beginning of this century the characterization of the species origin of bloodstains was made solely on the basis of the morphology of the red cells Although there are well recognized species differences in the size and shape of the intact mammalian erythrocyte, the effects of autolysis, hemolysis, drying and other mechanical distortion are such as to relegate this method of species identification to one of minor importance today

In 1901 Uhlenhuth² introduced the immunologic tests for human blood He showed that it was possible to prepare a specific antihuman rabbit serum by repeatedly injecting a rabbit with human blood The rabbit serum, when layered with a dilute solution of human blood, caused a precipitate to form at the interface The principle of this test forms the basis of present medicolegal tests for species identification of blood

Uhlenhuth's initial experiment was simple and qualitative It failed to reveal the fact that in many cases antisera against the blood of a particular animal also show cross reactions with the blood of other animals Thus, antihuman serum will probably react with the blood of monkeys and apes, and will occasionally react with the bloods of many other animals, even those remotely related These cross reactions are dependent upon a number of factors, some of which are not understood At present there is no certain method of preparing a high-titer specific antiserum by the use of a single animal Some animals fail to produce strong antisera, others produce antisera that are non-specific

The specificity of an antiserum may be improved by absorption of the undesired antibodies³ If an antihuman serum is found to exhibit an undesired cross reaction with dog blood, it may be mixed with dilute dog blood, allowed to stand several hours and then centrifuged The resulting serum will no longer react with dog blood, but will retain

its antihuman properties By such absorption it is likely that much of the "general animal" antibodies will be removed also, and that undesired cross reactions with any other animal bloods will be reduced greatly In other words, nonspecific antibodies tend to be nonspecifically absorbed

Because human blood is a complex mixture of proteins, antihuman-blood rabbit serum contains a mixture of antibodies Some of these are capable of reacting with most of the soluble proteins of human origin, regardless of whether they are blood or not Wiener⁴ has suggested the use of antihuman hemoglobin serums instead These may be prepared by injection of rabbits with washed, laked human erythrocytes It is then possible to identify human blood in one simple test, without the necessity of preliminary chemical tests to establish the presence of hemoglobin Hemoglobin is a poor antigen, with it the production of strong antisera is difficult However, the inconvenience in preparation of antihuman hemoglobin serum is outweighed by the advantages gained in its use

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JOSEPH T WALKER, PH D

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mospheric pressure, the mode of entry and action of toxic
materials, sampling and analysis of atmospheric contami-
nants, radiant energy and radium (including poisoning by
radium and thorium), ventilation, occupational dermatoses,
the visible marks of occupation and occupational diseases,
fire and explosion hazards of combustible gases, vapors and
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All doctors of medicine interested in surgery are invited.
Further information regarding the program may be obtained
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New Jersey.

Such shocking exhibitions of dyed heads as are occasionally met with in the streets, in this change loving age, when fashionable people think they can color their skins and their hair with as much ease as politicians turn their coats under a new administration, show the necessity of a more perfect and expeditious mode of accomplishing the metamorphosis

Boston M & S J, August 8, 1840

NOTES FROM THE MEDICAL EXAMINER

IDENTIFICATION OF BLOODSTAINS — II

The proof that a stain has been caused by blood is a significant step in its identification.¹ To show that it has been caused by human blood is of much greater importance.

Before the beginning of this century the characterization of the species origin of bloodstains was made solely on the basis of the morphology of the red cells. Although there are well recognized species differences in the size and shape of the intact mammalian erythrocyte, the effects of autolysis, hemolysis, drying and other mechanical distortion are such as to relegate this method of species identification to one of minor importance today.

In 1901 Uhlenhuth² introduced the immunologic tests for human blood. He showed that it was possible to prepare a specific antihuman rabbit serum by repeatedly injecting a rabbit with human blood. The rabbit serum, when layered with a dilute solution of human blood, caused a precipitate to form at the interface. The principle of this test forms the basis of present medicolegal tests for species identification of blood.

Uhlenhuth's initial experiment was simple and qualitative. It failed to reveal the fact that in many cases antisera against the blood of a particular animal also show cross reactions with the blood of other animals. Thus, antihuman serum will probably react with the blood of monkeys and apes, and will occasionally react with the bloods of many other animals, even those remotely related. These cross reactions are dependent upon a number of factors, some of which are not understood. At present there is no certain method of preparing a high-titer specific antiserum by the use of a single animal. Some animals fail to produce strong antisera, others produce antisera that are non-specific.

The specificity of an antiserum may be improved by absorption of the undesired antibodies.³ If an antihuman serum is found to exhibit an undesired cross reaction with dog blood, it may be mixed with dilute dog blood, allowed to stand several hours and then centrifuged. The resulting serum will no longer react with dog blood, but will retain

its antihuman properties. By such absorption it is likely that much of the "general animal" antibodies will be removed also, and that undesired cross reactions with any other animal bloods will be reduced greatly. In other words, nonspecific antibodies tend to be nonspecifically absorbed.

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AMERICAN ACADEMY OF GENERAL PRACTICE

The American Academy of General Practice will hold its second Scientific Assembly in St. Louis, Missouri, on February 20-23, 1950. Further information may be obtained by writing Mr. Mac F. Cahal, Executive Secretary, 406 West Thirty-Fourth Street, Kansas City 2, Missouri.

GRANTS AND FELLOWSHIPS IN
CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is accepting applications for grants and fellowships. Applications for new grants in cancer research will be received until October 1. Investigators now receiving grants will be notified individually regarding application for the extension of these grants. Final decision on applications will be made in most cases soon after February 1, 1950. Grants approved at this time ordinarily will become effective July 1, 1950.

Fellowship applications may be submitted at any time. Those received prior to November 1 will be acted upon by the Committee on Growth in December. Those received between November 1 and March 1 will be acted upon in April. Fellowships ordinarily will begin July 1, though this date may be varied at the request of the applicant.

During the past year the American Cancer Society, Inc., on recommendation of the Committee on Growth, has approved research grants and fellowships totaling over \$2,000,000.

Communications regarding grants and fellowships should be addressed to Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

SHORT-TERM DUTY AVAILABLE FOR
ARMY MEDICAL RESERVISTS

The Department of the Army has recently published Special Regulation 140-210-10, which authorizes commanders of Army installations to place volunteer reserve officers of the Medical, Dental, and Veterinary Corps on active duty for periods of from 1 to 29 days a month, but not more than 90 days of active duty in a fiscal year. Officers selected will be placed on active duty in the grade in which currently commissioned in the Officers' Reserve Corps.

Active duty will be performed at an Army installation or activity situated within the vicinity of the officer's home. No officer will be ordered to active duty where travel to duty station is involved. However, authorization whereby officers may volunteer as ship's surgeon on an Army transport for a round-trip voyage is given in the regulations.

ASSOCIATION OF SCHOOL PHYSICIANS

The interim committee appointed at the Amherst meeting convened at Hotel Sheraton, Worcester, on July 24. School physicians should watch these columns and those of the *Newsletter* of the Massachusetts Department of Public Health for notices and announcements.

ALVARENGA PRIZE

On July 14, 1949, the College of Physicians of Philadelphia awarded the Alvarenga Prize for 1949 to Owen Harding Wangensteen, M.D., Ph.D., professor of surgery, University of Minnesota, for his contributions to the etiology and therapy of gastric and duodenal ulcer. Dr. Wangensteen will deliver the Alvarenga Lecture on this subject at the College of Physicians of Philadelphia on November 2.

The Alvarenga Prize was established by the will of Pedro Francisco da Costa Alvarenga, of Lisbon, Portugal, an associate fellow of the College of Physicians of Philadelphia to be awarded annually by the College of Physicians on the anniversary of the death of the testator, July 14, 1883.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 6-10 American Congress of Physical Medicine Page xiii, issue of March 24

SEPTEMBER 8 Care of the Terminal Stage of Cancer Dr. John W. Spellman, Pentucket Association of Physicians 8:30 p.m., Haverhill

SEPTEMBER 28 New England Pediatric Society Page 136, issue of July 21

SEPTEMBER 28-30 Mississippi Valley Medical Society Page xi, issue of July 14

OCTOBER 11-15 American Society of Clinical Pathologists, Drake Hotel, Chicago

OCTOBER 24-26 National Gastroenterological Association Page 251

OCTOBER 24-28 American Public Health Association Page 251

NOVEMBER 2 New England Obstetrical and Gynecological Society, Hotel Somerset, Boston

NOVEMBER 2-5 Pan-American Congress of Pediatrics Page 231

NOVEMBER 3-5 American Association of Blood Banks Page xi, issue of June 16

NOVEMBER 7-9 National Society for Crippled Children and Adults Page 184, issue of July 28

NOVEMBER 7-12 International College of Surgeons Page 231

NOVEMBER 14-17 American Academy of Pediatrics Page 231

FEBRUARY 20-23 American Academy of General Practice Notice above

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING
THURSDAY, AUGUST 18

FRIDAY, AUGUST 19

*9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds, Peter Bent Brigham Hospital

*1:30 p.m. Tumor Clinic, Out Patient Department, Mt. Auburn Hospital, Cambridge

MONDAY, AUGUST 22

*11:30 a.m.-12:15 p.m. Chest X-Ray Conference, South End Health Unit, 57 East Concord Street, Boston. Dr. Cleveland Floyd in charge

*12:15-1:15 p.m. Clinicopathological Conference, Main Amphitheater, Peter Bent Brigham Hospital

TUESDAY, AUGUST 23

*12:15-1:15 p.m. Clinicoradiological Conference, Peter Bent Brigham Hospital

*1:30-2:30 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital

WEDNESDAY, AUGUST 24

*12:00 p.m.-1:00 p.m. Clinical Conference, (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital

*Open to the medical profession



*When summer brings green apple days
And the children are running both ways,
Dr. Wise shortly finds
A stout potion that binds —
In the ads that the Journal displays*

The New England Journal of Medicine

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Volume 241

AUGUST 18 1949

Number 7

ROSEOLA INFANTUM (EXANTHEM SUBITUM)*

WILLIAM BERENBERG M.D.,† STANLEY WRIGHT M.D.,‡ AND CHARLES A. JANEWAY M.D.§

BOSTON

THE problem of fever in infancy is one of the most common and difficult ones confronting the general practitioner and pediatrician. In 1910 Zahorsky¹ described a febrile exanthem occurring in infants and young children which he termed roseola infantum. This disease was characterized by a relatively asymptomatic febrile course of three to five days, followed by the appearance of a morbilliform eruption. Several years later Veeder² helped confirm this syndrome as a specific pathologic entity and suggested the name exanthem subitum. Since that time the disease has attracted wide interest in pediatric circles. However, since patients afflicted with this condition are rarely seriously ill or hospitalized, the average medical student does not see many cases and consequently roseola has become to many physicians an unfamiliar, little appreciated disease that is frequently misdiagnosed or unrecognized. The name roseola itself has been something of a handicap since it is so easily confused with the terms rubeola (measles) and rubella (German measles). This is all the more surprising since there is increasing evidence that roseola is probably the most common febrile exanthem in children and infants under three years of age.³

During the ten-year period 1937-1947 181 cases were seen at the Children's and Infants' hospitals, Boston. This group is hardly representative of the type of disease ordinarily encountered in practice since the average patient is not ill enough to be referred to a hospital for care. It is in great measure made up of children who have had convulsions, who have been more prostrated than usual, or in whom the duration of the febrile stage has been unusually protracted. In order to make the following descriptive discussion more typical of what may be expected, we have also drawn on their own experience

in practice as well as on the various descriptions in the literature.

FREQUENCY

Many authors⁴⁻⁷ have commented on the surprising frequency with which they encountered roseola in their own practice once they were on the lookout for the condition. Breese³ followed 70 newborn babies for a year with special attention to the number who developed roseola, and observed 11 cases, an incidence of 16 per cent. In view of the age-distribution curve he concludes that approximately 30 per cent of all children develop the disease eventually. In our own experience it has been the most common exanthem encountered under two years of age. As pointed out below, there is reason to suspect that the disease may be almost universal in one form or another under the age of five years.

SEASONAL INCIDENCE

Roseola may occur in any month of the year although it appears to be most prevalent in late spring and mid-autumn.^{2, 5} In patients admitted to the Children's Hospital the peak months were May and October.

SEX AND AGE INCIDENCE

No difference in incidence between the sexes was observed. As is implied in its name, roseola infantum is principally a disease of infants and young children. In our own series the youngest patient seen was four months of age, and the oldest eight years. All those who have described this disease are in complete agreement about the general age-distribution curve (Fig. 1) fully 95 per cent of cases occurring between the ages of six months and three years. Zahorsky¹ refers to a case seen when the patient was two weeks old, and Cutts¹⁰ describes a typical example in a woman of thirty-one years.

PREFEBRILE PRODROMES

These are almost invariably absent, although occasionally the child may have short periods of unimpressive, ill defined irritability and malaise.

*From the Department of Pediatrics, Harvard Medical School, and the Children's and Infants' hospitals, the Children's Medical Center.
†Instructor in Pediatrics, Harvard Medical School; associate physician, Children's and Infants' hospitals.
‡Member, Department of Pediatrics, University of Rochester; Rochester, New York; formerly assistant resident physician, Children's and Infants' hospitals.
§Thomas Morgan Roach, Professor of Pediatrics, Harvard Medical School; physician-in-chief, Children's and Infants' hospitals.

ONSET

The onset is usually abrupt from the point of view of fever. The child may be slightly irritable

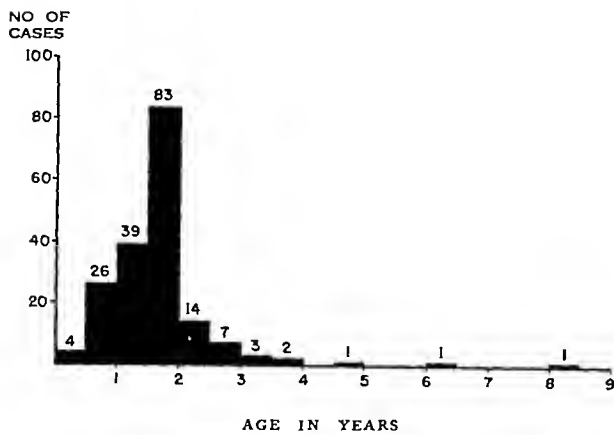


FIGURE 1 Age Distribution in Roseola (181 Cases, 1937-1947)

or listless, but the mother's attention is ordinarily first attracted to him because he feels warm. On taking the temperature she is usually surprised to

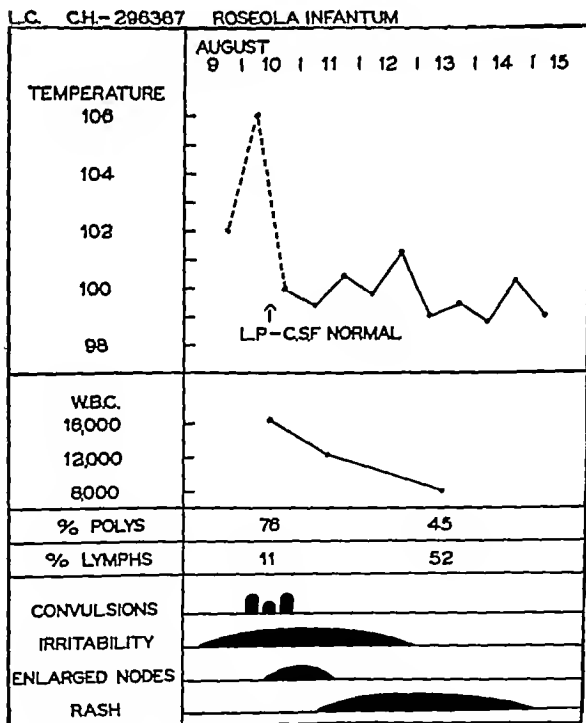


FIGURE 2 Clinical Course in Roseola, with Drop in Temperature by Crisis

find it elevated to 103 to 105°F. The patient, despite the high fever, is most commonly active and alert, and appears quite well.

CLINICAL COURSE

The course of the disease is chiefly characterized by a constant or intermittent, high fever for three to five days. Less often the fever persists for as long as seven to nine days. The temperature is often normal or slightly elevated in the morning, only to rise to 104 to 105°F by early evening. Generally, the patient appears relatively well, although with the increase in fever he may become restless, irritable, listless or wakeful. Older children may complain of headache and abdominal pain.

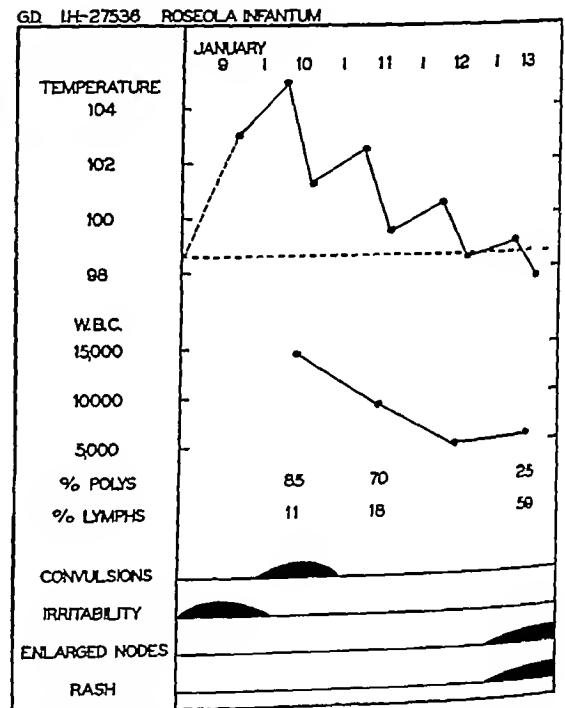


FIGURE 3 Clinical Course in Roseola, with Drop in Temperature by Lysis

In most cases the only symptoms are those which might be directly ascribed to fever itself irrespective of the cause. Appetite is ordinarily but slightly impaired, and vomiting may occur if large amounts of foods are ingested while the patient is febrile. A fair proportion of our patients had mild coryza or cough, but the interpretation of this was difficult since many cases occurred during the season when upper respiratory infections were prevalent in the community. The temperature usually drops to normal by crisis coincident with or immediately preceding the appearance of the rash. In a smaller number of cases, especially those with intermittent fever, a fall in temperature by lysis may occur over a period of twenty-four to thirty-six hours (Fig 2 and 3).

PHYSICAL FINDINGS

There is usually a paucity of physical findings, and those present are neither diagnostic nor constant

General Appearance

Almost all patients look and act quite well. They are usually alert, happy and playful. With unusually high fever they may appear listless or irritable, as previously described above. In a very small number of cases they are acutely ill and prostrated, and are occasionally seen in apparent collapse.

Pulse and Respirations

These are usually elevated in proportion to the fever and show no special features.

Pharyngitis

Fully a third of our patients had some mild diffuse catarrhal inflammatory reaction of the pharyngeal mucosa. This was never striking enough to make the examiner satisfied to ascribe the fever to bacterial pharyngitis.

Tonsillitis

A small number of patients with typical roseola have a well defined tonsillar inflammation with occasional exudative follicles. These have developed while the patients were on chemotherapy, and direct cultures even in untreated patients have yielded no significant pathogens. These observations suggest that tonsillar involvement may be due to the roseola virus although there is no reason to doubt that coexistent or secondary bacterial infection does occur.

Enanthem

There is no true or constant enanthem in this disease. However an increasing number of patients have been found¹¹ who exhibit what are apparently areas of lymphoid hyperplasia in the region of the uvula and soft palate. In our experience these appear to consist of pin-point elevations on the mucous membrane that are slightly pinker in color than the surrounding mucosa. They are only rarely striking and are easily missed unless the examiner looks specifically for them with adequate illumination. They may appear at any time during the first few days of the disease and usually persist for a few days beyond the appearance of the rash.

Otitis

About a quarter of our patients demonstrated a mild catarrhal otitis media, which was considered to be a reflection of the type of inflammatory pharyngeal reaction just described. This was not ordinarily associated with significant pain and subsided rapidly without specific therapy. Extensive catarrhal otitis or suppurative change developed in relatively few patients, and it was believed that

these represented secondary or coexistent bacterial invasion. Cultural studies failed to reveal the constant presence of any particular organism in the small group who required paracentesis or drained spontaneously.

Pulmonary Changes

Physical examination of the lungs has not revealed any significant abnormalities. In a small percentage of the more severely ill patients we have observed nonspecific increase in interstitial pulmonary markings by roentgenographic examination. The significance of this observation is open to question in view of the normal roentgenograms obtained in the majority of patients so examined.

Lymphadenopathy

The importance and incidence of significant lymph-node enlargement has long been debated. Various authors^{5, 11, 12} have maintained that suboccipital, posterior cervical and postauricular adenopathy is a frequent and important finding. Others^{2, 3, 13, 14} have been unable to confirm this observation. It has also been pointed out¹⁵ that although suboccipital adenopathy is frequent in roseola, the other causes of lymph-node enlargement in this region in childhood are so common that its true significance is open to question. Much of this confusion may be explained by the inadequacy of reviews of hospital records in this respect unless the various observers were especially interested in looking for such changes and specifically recorded their absence as well as presence. In 70 cases in our series in which the patients were examined carefully and repeatedly for adenopathy, some enlargement of suboccipital or posterior cervical lymph nodes was nearly always demonstrable. The degree of enlargement was variable but was considered to be obviously significant in the majority of cases. It was also noted that in many cases the lymph nodes first became palpable on the second or third day of disease and continued to increase in size over the next few days. They rarely reached a size of more than 0.5 to 1.5 cm. The nodes are usually moderately firm, nontender and freely movable. Enlargement may persist for several weeks.

Rash

It has been emphasized that roseola is the only exanthem typically characterized by a pre-eruptive period of high fever, after which the child becomes well when the rash erupts. The rash occurs predominantly on the neck and trunk only, although it may involve the proximal extremities, postaural regions and face. Its appearance ordinarily coincides with the subsidence of fever, or it may follow this by as much as thirty-six to forty-eight hours. As its name implies, the eruption is rose pink. It is characterized chiefly by discrete, small, often irregu-

lar-shaped macules, occasionally maculopapules, measuring 2 or 3 mm in diameter and fading on pressure. They have no tendency to grouping and are distinctly separated although on rare occasions with an extensive eruption they coalesce. The individual macules are often surrounded by a whitish areola. There is no pruritus or desquamation.⁶ The eruption usually lasts for twenty-four to forty-eight hours and then fades completely without residual pigmentation. We have seen a few typical cases in which the rash appeared and faded completely within two to four hours. This raises the obvious possibility of missing a rash that occurs in an area usually covered by clothing and may be relatively fleeting (Fig 4).

LABORATORY STUDIES

Blood

Although the white-cell count is classically described as being low in this condition, it is worth



FIGURE 4 Post-Febrile Skin Eruption in Roseola
Example of a rather florid eruption

emphasizing that if one sees the patient in the first twenty-four to thirty-six hours, some slight leukocytosis is the rule. During this period the white-cell count is usually in the range of 12,000 to 15,000, with a slight increase in neutrophils. Occasionally, counts are as high as 20,000 to 22,000 at this time. Ordinarily by the second day and invariably by the third day there is a definite leukopenia accompanied by an absolute neutropenia and a relative lymphocytosis. The white-cell count usually returns to normal within a week, but the lymphocytosis may persist for a longer period. No abnormal cells have been encountered on smear, and no changes in hemoglobin or red cells are demonstrable.

Nose and Throat Cultures

Almost all the patients in this series had such cultures with results similar to what one would expect to obtain from the nasopharyngeal flora of any comparable asymptomatic group of well children.

Cerebrospinal Fluid

Because of the high incidence of febrile convulsions in our series, many lumbar punctures were performed. All these spinal fluids were sterile and showed no alterations in sugar, globulin or quantitative protein. In only 1 case was any significant number of cells (25 lymphocytes per cubic millimeter) encountered.

Urine

Routine urine examinations, which were performed in most of the patients studied, showed no variations from the normal.

Virus Studies

Previous attempts³ to isolate a filterable agent have proved unsuccessful. In 6 of our patients studies¹⁶ were carried out on nasopharyngeal washings and cerebrospinal fluid collected during the febrile pre-eruptive stage, which were inoculated into mice intranasally, intracerebrally and intraperitoneally. Similar material was inoculated into chick embryos in 2 cases. To date, no specific viral agent has been isolated.

EPIDEMIOLOGY

The striking age incidence between six months and three years and the tendency for increased numbers of cases to appear in the spring and fall were noted above.

INCUBATION PERIOD

In 6 cases there was positive evidence of intimate exposure preceding the appearance of roseola, the incubation period was between ten and fifteen days as reported in two separate epidemics.^{7, 17} However, on 3 occasions the disease appeared thirty to ninety days after a known intimate exposure, without any history of subsequent contact. Garvin¹⁸ is stated to have observed cases of the disease forty-one days apart in twins, and Davies¹⁹ has seen cases one hundred and sixty days apart in siblings. The shorter incubation periods unquestionably are the more likely, especially since there is no proof that there was not an intermediate unknown exposure in cases occurring thirty to ninety days after contact. However, these long incubation periods are of considerable interest.

COMMUNICABILITY

Roseola is a disease of rather poorly defined communicability. There is rarely any spread to sib-

lings,²⁰ who are almost always outside the susceptible age group in the average family. All those engaged in pediatric practice are familiar with the minor waves of increased frequency of the disease on occasion. There almost never is any well defined epidemic spread, although 2 such cases are reported from foundling homes.^{7, 19} We have not seen the disease spread on the general wards of the Infants' Hospital, where these patients are cared for with the same gown precautions used on all infants.

IMMUNITY

In roseola as in all other exanthems, well established second cases of infection are reported,^{21, 22} although these are unusual. For all practical purposes one attack affords permanent immunity. Despite the claim of some early authors that roseola was an anomalous form of German measles¹² or measles, it has been well established that there is no cross immunity and that roseola stands as a specific entity.

ETIOLOGIC AGENT

Although no specific etiologic agent has ever been demonstrated, the incubation period, clinical course, blood changes, failure to respond to chemotherapy and immunologic concepts all lend credence to the idea that roseola is produced by a viral agent.

PROGNOSIS

As indicated above the prognosis in this disease is supposed to be excellent almost by definition. However, we have recently encountered several infants who became desperately ill at the height of the disease despite an early sense of well being. One ten-month-old infant, who fulfilled all the diagnostic criteria including subsequent typical rash, became critically ill on the second day of disease. He went into a shock-like state of collapse, with rapid, thready pulse, dyspnea, cyanosis and a cold, mottled skin. This did not appear to be due to hyperpyrexia. For a period of a few hours it appeared unlikely that he would survive, although he eventually responded to symptomatic shock therapy.

COMPLICATIONS

The commonest complication encountered in our series was convulsions. The actual incidence in hospital and consultation practice is quite high, and in some years convulsions occurred in as many as a third of the patients. This incidence is obviously false and artificial, for a convulsion was often the chief reason for hospitalizing the patient. It must be borne in mind that the vast majority of patients with roseola are never sufficiently ill to warrant hospital care or study. The incidence of convulsions has been variably reported as 0.7 per cent,¹⁸ 6 per cent²³ and 50 per cent,²⁴ depending on the source of material with the lowest incidence in cases reviewed in general practice and the highest

in hospital practice. The seizures are usually generalized, tonic or clonic in character, and of short duration, without sequelae. Presumably, they are febrile in origin. We have only observed alterations of cerebrospinal fluid in this group in 1 case. Lumbar puncture was performed on almost all the convulsive patients in our series. The occurrence of seizures was most common in patients in whom the onset was very abrupt, with sudden, unusually high fever.

Several patients appeared unusually drowsy after one or a series of convulsions. A relatively small number of patients were stuporous for one to twenty-four hours. An example of striking encephalitis in a twelve-year-old boy has been reported.²⁵

Two of our patients had postconvulsive hemiplegias, which cleared in two to five days respectively. A case in which such a hemiplegia persisted for ten weeks has been reported.²⁶ Such complications are almost certainly due to the preceding convulsions rather than to roseola per se.

DIFFERENTIAL DIAGNOSIS

The commonest error in diagnosis is to call the acute illness acute pharyngitis, otitis media or pneumonia and to ply the patient with unnecessary chemotherapeutic agents. The eruption is often misdiagnosed as a toxic rash, prickly heat or eczema. An important error in diagnosis is that of drug rash since it may affect the patient's care in a subsequent illness in which there is real need for chemotherapy. Often the attending physician prescribes one of the sulfonamides or penicillin in the absence of a specific diagnosis because of the unusually high fever. When the rash appears a diagnosis of drug rash is made, and the patient is erroneously labeled as sensitive to the chemotherapeutic agent. Drug rashes are more apt to be confluent and more widespread and less apt to be confined chiefly to the trunk as in roseola. If the medication is continued and the rash fades, the diagnosis of sensitivity may be eliminated.

The following exanthems are to be differentiated from roseola.

Chicken pox The vesicular character of this rash is unique enough so that erroneous diagnosis is unlikely.

Scarlet fever This usually has a shorter invasion period, more constant although less elevated temperature, more angina, tongue changes and febrile state of acute illness when the rash appears. The appearance of the rash is, of course, quite different, and neutrophilic leukocytosis is the rule.

Measles The presence of cough, coryza, Koplik spots, conjunctivitis and the intensification of fever and malaise with the appearance of the eruption should serve to differentiate this disease from roseola.

German measles The rash and lymphadenopathy here more closely resemble roseola than in any other condition. The rash of German measles is apt to be more widespread and may coalesce. Its frequent epidemic incidence is most helpful in diagnosis. The absence of a high temperature and the early appearance of the rash during the febrile stage should serve to differentiate this condition from roseola.

Infectious mononucleosis Approximately 5 to 10 per cent of patients with infectious mononucleosis develop a rubella-like rash or scarlatiniform eruption in the early febrile stage of the disease. The longer course, more striking and more generalized lymphadenopathy, splenomegaly and laboratory findings of many atypical lymphocytes on smear with the development of a positive heterophil-antibody agglutination should distinguish this condition.

TREATMENT

The treatment of roseola is purely symptomatic. The patient should be kept at rest and given fluids freely. Aspirin is helpful in keeping the patient more comfortable by virtue of its antipyretic effect. In patients with a sudden high temperature, phenobarbital may well be employed to raise the convulsive threshold and prevent seizures from occurring. The sulfonamides, penicillin and streptomycin are of no value.

DISCUSSION

Roseola infantum, a well defined, common exanthem of infancy and early childhood, has been recognized in approximately 15 to 30 per cent of children carefully followed by those familiar with the disease. The known factor of its incidence raises a number of interesting speculations concerning its epidemiology. The comparative infrequency of cases before the age of six months suggests transplacental passive immunization of the infant by its mother such as occurs in measles. On the other hand, the rarity of cases beyond the age of three years is unlike the situation in measles and is particularly remarkable in view of the demonstrated susceptibility of occasional older patients. It raises the possibility that almost all susceptible persons may be exposed and may contract the disease in the first three years of life. On the other hand, the infrequency of epidemics, suggesting that the degree of contagiousness is probably not high, is difficult to reconcile with such a concept.

This situation could be explained by widespread dissemination of the infective agent, perhaps by numerous adult carriers, universal susceptibility after disappearance of the antibodies received from the mother and the existence of atypical modified forms of the disease. In view of the manner of spread of the epidemics reported by Barenberg¹² and Cushing,⁷ it was concluded that the disease was

transmitted by adult carriers. If true, this would explain the sporadic occurrence of roseola and the usual absence of a known exposure.

The occurrence of asymptomatic, inapparent or very mild forms of infection has been recognized with other virus diseases such as poliomyelitis, infectious hepatitis and mumps. That this may occur in cases of roseola is quite possible. Moreover, it is logical to assume that, as in measles, there may be a period between four and eight months of age when immunity passively acquired from the mother gradually recedes. During this period the antibody titer may well be low enough to allow the infant to contract a modified form of the disease. All pediatricians have seen many infants and young children who acted as though they had roseola but in whom the rash was never demonstrated. Again, the rash may be so fleeting as to defy detection unless it is constantly watched for day and night. The idea that an atypical, mild, modified form of the disease exists is held by various authors.^{3, 11, 17} If adult carrier states are common, there may well be numerous cases of unrecognized modified infection occurring around the age of six months. Indeed, if these hypotheses are correct, it may not be too far fetched to assume an almost universal incidence of both recognizable and unrecognized modified disease in infancy and early childhood to explain the unusual occurrence of a common virus infection that is rarely seen before the age of six months or after the age of three years.

Although roseola is certainly a benign disease in the vast majority of cases, we have observed a small but definite number of patients with a more serious clinical picture. It hardly seems possible that a disease of infancy with such a marked febrile reaction should invariably be benign. As the disease is now defined and interpreted, it is dismissed from differential diagnostic consideration if the patient succumbs, and in such a case its recognition is impossible since its distinguishing feature, the rash, only appears at the time of clinical recovery. In view of some of our experiences, we have speculated that some cases of so-called "sudden death" in infancy may eventually be proved to be unusually severe, unrecognized forms of roseola. The chief pathological findings described by Farber²³ in many of his reported cases of sudden death were interstitial pneumonia and cerebral edema — lesions of a type that might be expected in a viral infection.

SUMMARY

1 Roseola infantum (exanthem subitum) is a relatively asymptomatic febrile disease, with a paucity of physical findings, of three to five days' duration followed by a morbilliform eruption.

2 It is the commonest exanthem of infancy. The hypothesis is offered that it may be an almost universal infection under the age of five years.

3 It is most prevalent in spring and autumn.

4 There is no difference in incidence between the sexes

5 Fully 95 per cent of cases occur between the ages of six months and three years

6 The clinical course, physical findings and hematologic changes are described

7 The incubation period is defined and the communicability and epidemiology discussed. The possibilities of a large carrier population and a modified form of the disease are raised

8 The evidence favors a viral etiologic agent

9 The prognosis is for the most part excellent. The possibility of the existence of more serious unrecognized and occasionally fatal variants of the usual clinical picture is raised

10 The recognized complications include convulsions, encephalitis and rarely hemiplegia

11 The disease can be differentiated from the other common exanthems

12 The treatment is purely symptomatic

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THE MAJOR UROLOGIC CONSIDERATIONS IN PARAPLEGIA*

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THE health of the upper urinary tract in paraplegia is, except for one hazard, dependent upon the health and function of the bladder. That exception is a tendency toward the formation of renal stones during prolonged recumbency or inactivity. But this tendency is itself greatly exaggerated by infection and stasis, both of which are sequelae of vesical dysfunction. From the hour of injury, therefore, there can be no temporizing with the care of the bladder if the dangerous consequences of the neurogenic disorder are to be averted or diminished.

After any severe spinal-cord injury, there is often a period of spinal shock. This is marked by the suppression of all reflex activity below the level of the injury. The bladder, sharing in this common suppression, is unable to evacuate its contents and

requires artificial drainage. It has generally been considered that the bladder is atonic during this period. Nesbit and Lapides¹ have suggested that the atony is not primary, but occurs only if, as a result of inadequate drainage, the bladder wall has become overdistended and decompensated. It may be that in such cases tonus is maintained through the agency of the intrinsic ganglions of the vesical wall. Munro,²⁻⁴ on the other hand, states that cystograms taken on many patients shortly after injury regularly reveal complete atony. One thing is quite apparent,—that in many cases, if not always, a return of tonus becomes evident before the detrusor is yet capable of the strong, sustained contractions necessary to bring about voiding. This return may be delayed or totally impeded by overdistention, the avoidance of which, therefore, becomes a chief aim of early treatment. For it must be apparent that a decompensated bladder wall may in time undergo changes that will irreversibly alter its functional capacity.

A concept thus emerges that has not been emphasized in the literature on this subject—that the alterations in function following interference

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with the nerve supply of the bladder must be interpreted in terms of an organ that has also been subjected to other drastic structural alterations. There may come a time when, even if the innervation might be miraculously restored, the functional result would still be poor. The avoidance and treatment of such alterations, whether they come early or late, then becomes a major factor in the urologic care of these patients.

During the war, there was some justification for the performance of early cystostomies in forward areas. In civilian conditions, there is none. Catheter drainage with tidal irrigation is easily the method of choice. Permanent suprapubic cystostomy has fewer and fewer advocates as time passes, and as attention focuses more sharply upon true rehabilitative treatment rather than mere expediency.

With the patient's emergence from the phase of spinal shock, the bladder almost invariably resumes its reflex activity. Exceptions occur when the spinal reflex centers have themselves been destroyed, leaving an autonomous bladder, or when the bladder wall has so changed as to be incapable of normal response to the stimuli directed to it. Such changes may be the result of prolonged or excessive distention, contraction such as frequently follows prolonged suprapubic drainage, or infection with consequent fibrosis. The reflexly acting bladder is that which is commonly called "automatic," an unfortunate term, since it does not accurately describe the functional status. Correctly designated, an autonomous bladder is one that has been completely divorced from the central nervous system by destruction of the spinal reflex center that mediates micturition, or by interruption of the fibers concerned in the reflex arc. It has a fairly characteristic pattern of behavior—hypertonicity with frequent ineffectual contractions. It is always leaking but never empty. The neural function is mediated through the ganglions within the vesical wall, aided by the intrinsic response of smooth muscle to the stimulus of stretch. This type of bladder is characteristically associated with destructive lesions of the sacral segments and the cauda equina.

The re-establishment of satisfactory function of the reflex bladder postulates urethral voiding, a bladder of sufficient capacity to act as a reservoir for convenient intervals and with reasonable consistency, a bladder that is capable of emptying itself completely or almost completely, and a sufficient degree of control to avoid involuntary escape of urine. Satisfactory urethral voiding involves the closure of all fistulas whether of deliberate or accidental origin. The latter are usually the result of infection, most often penurethral, they generally emerge at the penoscrotal junction and practically always require surgical repair. Occasionally they are seen in association with urethral diverticula. A previously established suprapubic

sinus that does not heal promptly during urethral catheter drainage should have a definitive surgical closure. Pate and Bunts⁵ have described two cases of fatal peritonitis in patients in whom the fistula had closed at the abdominal wall but had not become completely obliterated. Such occurrences illustrate the danger inherent in spontaneous closure of a long-standing fistula.

The bladder capacity need not be excessive, 8-10 ounces (240-300 cc.) is quite satisfactory, and 7 ounces (210 cc.) is probably safer. The greater inconvenience of slightly more frequent emptying is amply compensated for by avoidance of the hazards of overdistention. The only known stimulus to detrusor contraction, and thus to the emptying of the bladder, is stretch. This is a dynamic rather than a static phenomenon. It is dependent upon increasing intravesical pressure. Normally, the contractions thus elicited can be inhibited by impulses from higher centers. This inhibitory mechanism is the chief agent of voluntary control of micturition. Another is the voluntary contraction of the external sphincter, which is always accompanied by reflex inhibition of the detrusor. In the paraplegic patient, both these voluntary control mechanisms are commonly lost, and the bladder has returned to a state of uninhibited reflex function similar to that of infancy. The inhibitory impulses, however, are perhaps not the only manifestations of control from higher levels impinging upon the reflex center for micturition. The control of tonus, as well as certain co-ordinating and integrating factors are also, according to some observers, transmitted along descending fibers.⁶⁻⁹ Possibly as a result of their interruption, the reflex bladder may be hypertonic to a greater or lesser degree, and its detrusor, although it contracts powerfully, does so with diminished efficiency.¹⁰ In order to establish regularity and consistency of function, the familiar phenomenon of the conditioned reflex is invoked, through the use of tidal drainage and habit training, as first recommended by Munro,^{2, 4, 11, 12} and now widely adopted. The hygienic value of tidal drainage constitutes a further advantage in its use.

The occasional paradox of a hypertonic bladder that cannot empty itself completely is readily resolved. Lack of co-ordination and integration of detrusor activity has already been mentioned as a factor in dysfunction. This is most prominent in the autonomous bladder. The internal orifice, which is in fact the edge of the detrusor, shares in the hypertrophy due to frequent ineffectual contractions. This may be of sufficient degree to produce obstruction at the vesical neck. Superimposed infection or fibrosis, or both, may cause rigidity, contributing further to dysfunction. The opening of the internal orifice is a reciprocal concomitant of detrusor contraction resulting from the mechanical arrangement of the muscle fibers. It is probably

incorrect, certainly incomplete, to ascribe micturitional dysfunction to so-called neurogenic sphincteric disturbance. When persistent residual urine exists in association with bladder-neck obstruction, transurethral resection is indicated.^{13, 14} Even when such obstruction cannot be demonstrated cystoscopically, but when in spite of a good detrusor there is residual urine or retention of urine, resection is justified. Spasm of the external sphincter has been described¹⁵ and should be excluded before surgery is undertaken, but the importance of this phenomenon as an obstacle to voiding has not yet been conclusively demonstrated.

When a satisfactory and reasonably consistent capacity has been achieved and when the bladder empties itself completely, there remains the question of control. The problem is to train the patient to void at his own convenience, anticipating the involuntary reflex emptying of the bladder. Obviously, the patient must be able, first, to initiate micturition and, second, to know when to do so. Fortunately, a majority of paraplegic patients retain some degree of sensation associated with vesical filling. This may manifest itself in various ways. Some experience a suprapubic or generalized abdominal pain or a burning referred to the penile urethra. Others exhibit autonomic reactions such as sweating, chills or headache. A number, however, have no sensory recognition of a full bladder. Among this group, reliance must be placed on timing, with due attention to the regulation of fluid intake. An emptying contraction of the detrusor is initiated when the stimulus of stretch reaches an intensity sufficient to send an impulse along the afferent limb of the reflex arc. A useful means of bringing this to pass is by straining. This produces an increased intra-abdominal pressure, which is in turn transmitted to the bladder, there, the increased intravesical pressure produces the stretch stimulus, which sets off the voiding reflex. If the abdominal muscles are inadequate, a suitable belt may help. Tapping the abdominal wall, scratching the thigh, pinching the glans and other so-called "trigger" mechanisms are frequently used, but they are less physiologic and, generally, less dependable methods of stimulating bladder contraction. Direct manual pressure against the abdominal wall may reinforce the detrusor in the emptying of the bladder.

Before leaving this brief discussion of bladder function, one should note that other mechanisms have been described. Most recently, Mueller and Fleischer¹⁶ have demonstrated activity of voluntary muscles of the pelvic floor during the beginning of micturition, which they interpret as the initiating factor. It seems more probable, however, that such activity is of an auxiliary character.

Along with the care and training of the bladder, there are a number of collateral urologic problems affecting paraplegic patients. Renal calculi, of

less frequent occurrence than a few years ago, are occasionally encountered in patients returning after months or years at home. Pyonephrosis is a not uncommon complication. Treatment is not peculiar to paraplegia except, perhaps, for a greater than usual preoccupation with the conservation of renal tissue. Vesical calculi are treated by cystolitholapaxy without particular difficulty. Their occurrence or recurrence can often be averted by the establishment of good drainage, or by the use of suitable irrigating solutions when there is an indwelling catheter.

Chronic pyelonephritis is common. Bacteriuria is almost universal, but fortunately often exists without accompanying clinical evidence of infection, and with little or no pyuria. The organisms generally cultivated are the gram-negative bacilli, which are resistant to penicillin and respond but indifferently to the sulfonamides and streptomycin. For treatment over a long period, acidulation is useful when it can be achieved, with occasional courses of mandelic acid.

When renal infection becomes clinically apparent, appropriate investigation will reveal coexisting mechanical factors or structural changes in many cases. Notable among these is vesicoureteral reflux with hydroureter and hydronephrosis. The present view of the etiology of this condition is that it results not from neurogenic disturbance but from actual alteration of the ureterovesical orifice arising from chronic infection and distortion of the bladder wall.¹⁷ In the effort to correct this, two types of surgical approach have been employed. In one, the ureter is reimplanted into the bladder, in the other a complete lysis of the intravesical portion of the ureter is attempted. Too few cases have been treated so far to warrant any report on results.

Although hypertonicity of some degree is more common, hypotonic or even atonic bladders are encountered in paraplegic patients from time to time. On the basis of the assumption that this might be due to the physical state of the bladder wall itself, rather than the neurogenic factor, the size of the bladder was reduced, in 1 patient, by wide excision of the anterior wall. This man now has a normal capacity, can initiate micturition and has no residual urine. A second patient, subjected to a similar operation, has not yet reached the stage of trying to void, but already shows striking cystometric evidence of restored detrusor function.

Wherever there is extensive use of indwelling catheters, there will be a certain incidence of epididymitis, although meticulous technics may hold it down. Probably the best single prophylactic measure is the use of a small size catheter, preferably No. 16 Fr., and certainly not larger than No. 18 Fr. Prophylactic vasectomy is not desirable among

young men, many of whom retain sexual potency. After recurrent attacks of epididymitis, however, it is probable that the genital passages are effectively blocked, and that further exacerbation can best be prevented by epididymectomy. The chief danger of these recurring attacks is secondary involvement of the testicle and its ultimate destruction. One such case, which will be reported in detail at a later date, resulted in a fulminating, rapidly fatal septicemia. Vesicoureteral reflux, already mentioned, which is far more dangerous to health and life, seems to be slightly more frequent among patients who have had suprapubic cystostomies than among those who have not. Obviously, none of our present methods approaches perfection, but improving results justify the hope that continued effort and study may yet lead to further progress.

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MUMPS COMPLICATED BY A PRECEDING MYELITIS*

Report of a Fatal Case

A CLEMENT SILVERMAN, M.D.†

SYRACUSE, NEW YORK

WHEN McKaig and Woltman,¹ of the Mayo Clinic, published their review of neurologic complications of mumps in 1934, they reported a case of transverse myelitis in a sixteen-year-old girl who was left with a complete flaccid atrophic paralysis below the second thoracic segment. Her spinal fluid, incidentally, showed no increase in cells in two tests during her illness. The authors found a similar case of mumps myelitis in the literature in a girl one year older. Wesselhoef² cites these 2 cases and adds a case of myelitis with recovery from the French literature. Bobeff and Petroff,³ of Sofia University, Bulgaria, report mumps myelitis with residua in a six-year-old girl and mention 5 other cases from the literature, remarking that it is significant that there is no mention of this complication in the seventeen-volume work of Bumke and

Foerster⁴ (1935-36). In the same year (1941) Donohue⁵ reviewed the pathology of mumps encephalitis. Among the 10 autopsies analyzed, besides his own case, there were 2 cases of myelitis in a man of thirty-eight with parotitis and orchitis, in the other, a woman of thirty-four, death occurred more than a year after quadriplegia had followed mumps. The anterior-horn cells of the cervical and lumbar enlargements showed marked atrophy and degeneration and the corresponding peripheral nerves demonstrated degeneration of their axis cylinders and disappearance of myelin. Donohue doubted, however, that this neuropathological picture had any etiologic relation to mumps. Van Rooyen and Rhodes⁶ refer to seven reports of mumps myelitis. Two cases with recovery are described by Lightwood⁷ and Church.⁸ When duplications are omitted, there are references to 12 recorded cases of myelitis, with 2 autopsies. It thus appears that myelitis is perhaps the rarest of the neurologic

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involvements in mumps. It should be added, though, that undoubtedly many an unusual case occurs without being reported in the literature. In the Syracuse City Hospital, for example, a seven-year-old boy was admitted in 1938 with transverse myelitis following mumps. The case reported below is the second in almost nineteen years, among nearly 12,000 admissions for all causes*.

CASE REPORT

H G M., a 37-year-old physician, was admitted to City Hospital on June 19, 1947.

The day before, when making a call about noon, he found himself unable to shake down the thermometer readily. About 3 hours later he noticed in climbing stairs that the right leg seemed weak. In the evening while at a dinner he twice lost his balance and jokingly remarked that people might think he had been drinking. While making a call later that evening, he found it difficult to steer the car. He slept very little that night, being apprehensive that he was coming down with Landry's paralysis. Before morning he managed to go downstairs to his office to arrange as many of his affairs as possible because of his premonition. On the same morning he felt much weaker in both arms and legs, fell readily and had extreme difficulty in getting up, but could stand once he got on his feet. His wife took him to the hospital, and he managed to get out of the car and stand beside it, but when he attempted to go forward he fell and had to be lifted into a wheel chair.

He had always been in excellent health. In childhood he had had chicken pox, diphtheria, measles, rubella, scarlet fever and whooping cough but not mumps. A sister had had mumps, but he was away at the time, he thought. He had served as a medical officer with mountain troops in Italy during the war, he had had an attack of acute appendicitis there and had been operated upon uneventfully. For the past several weeks he had been working hard and felt tired out. There had recently been a number of cases of mumps in his area, and he had seen 2 cases with meningoencephalitis, 1 of which he had referred to the City Hospital 1 week before.

Physical examination showed an obviously anxious and apprehensive man, with no abnormal findings aside from the neurologic signs. There was no nuchal rigidity and no difficulty in swallowing. Respiratory movements appeared normal. There was generalized weakness in both upper and lower extremities. The biceps and triceps reflexes were diminished bilaterally. The right thigh was weaker than the left, but the reflexes were present. The abdominal reflexes were weakly present.

The temperature was 99.6°F by rectum, the pulse 64, and the respirations 20. The blood pressure was 125/75.

On an epidemiologic basis, the myelitis was considered due to mumps but without parotitis, and this diagnosis was offered the patient as affording a much better prognosis than Landry's paralysis.

A more complete neurologic examination was made later in the day and paralysis and paresis of most of the skeletal musculature were found. Superficial and deep sensation was not involved. There was no sign of meningeal irritation. The flexors of the neck were markedly weak. The cranial nerves were normal except for loss of the pharyngeal reflex.

Lumbar puncture yielded a clear spinal fluid without increased pressure containing 15 lymphocytes per cubic millimeter. The protein was 51, the sugar 79, and the chloride 750 mg per 100 cc. Spinal-fluid Wassermann, gum-mastic and colloidal-gold tests were negative.

Examination of the blood disclosed a red-cell count of 5,020,000 with a hemoglobin of 15.5 gm, and a white-cell count of 10,700, with 71 per cent neutrophils (10 per cent nonfilamented), 22 per cent lymphocytes, 6 per cent mononuclears and 1 per cent basophils. The urine was yellowish, clear and alkaline, with a specific gravity of 1.002. Tests for albumin and sugar were negative, and the sediment was

normal. Specimens of serum and spinal fluid were frozen and sent to the virus laboratory, Division of Laboratories and Research, New York State Department of Health.

During the next 2 days, the deep reflexes disappeared entirely, and the muscle weakness took the form of a complete quadriplegia. At no time was there a Babinski sign. The patient appeared more uncomfortable, restless and apprehensive. On June 21 bilateral parotid swelling appeared, somewhat greater on the right side. Next day he complained of pain in the legs but was able to move his feet a little and his shoulders very slightly. On the 5th day, he seemed more cheerful and somewhat encouraged. Hot packs to the muscles seemed to make him more comfortable. On this day the left parotid swelling was more prominent than the right.

On the next day he was more restless and apprehensive, having had a poor night. He was expectorating mucus

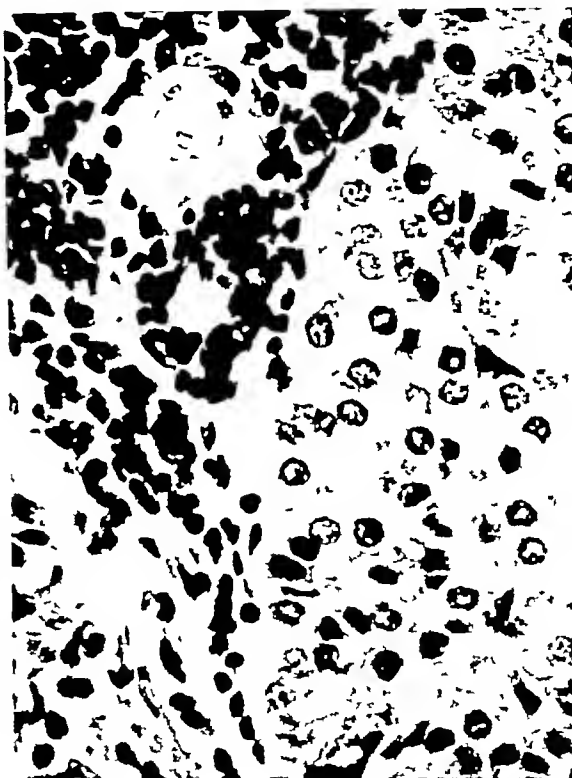


FIGURE 1 Section from the Parotid Gland, Showing Focal Lymphocytic Infiltration, Preservation of General Acinar Morphology and Pyknosis of Some Nuclei ($\times 800$)

but felt that he had more than he could bring up, and suction had to be performed frequently. The soft palate was normally movable, and there was no nasal twang and no fluid accumulation in the throat. He ate soft food and drank fluids without difficulty. In the night, however, he seemed unable to raise mucus, and his color was slightly dusky. Respiratory amplitude was unaffected. Oxygen was started by nasal catheter, and later that night the trachea was suctioned.

From this time on, the patient's condition and color continued poor, and he grew steadily worse. The temperature, which had previously remained normal, began to rise slightly. He was placed in an oxygen tent. Fluids were given intravenously, and also plasma and blood. Penicillin was started. Continual suctioning was required. On the evening of June 25 tracheotomy was performed, but the patient's color did not improve appreciably. He became confused and dis-

*Involvement of the central nervous system in mumps is a relatively common complication depending on the criteria employed for the diagnosis (whether on the basis of clinical findings, spinal fluid pleocytosis or chemical changes) and is usually quite benign so that fatal cases are extremely rare.

young men, many of whom retain sexual potency. After recurrent attacks of epididymitis, however, it is probable that the genital passages are effectively blocked, and that further exacerbation can best be prevented by epididymectomy. The chief danger of these recurring attacks is secondary involvement of the testicle and its ultimate destruction. One such case, which will be reported in detail at a later date, resulted in a fulminating, rapidly fatal septicemia. Vesicoureteral reflux, already mentioned, which is far more dangerous to health and life, seems to be slightly more frequent among patients who have had suprapubic cystostomies than among those who have not. Obviously, none of our present methods approaches perfection, but improving results justify the hope that continued effort and study may yet lead to further progress.

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also the virus of lymphocytic choriomeningitis. Isolation of mumps virus was also attempted by inoculation of embryonated hen's eggs via the amniotic and yolk-sac routes. None of the animals showed any signs of illness, nor could the virus be isolated from the embryonated hen's eggs. Blind passages were done in both instances. The fourth-passage amniotic fluid from amniotically inoculated eggs was used as antigen in a complement fixation with known positive mumps serum. Normal amniotic fluid and fluid containing mumps virus were used as negative and positive controls respectively. This test, which is quite sensitive, failed to reveal mumps virus.

The serum specimen taken on June 19 was tested with mumps antigen in the complement-fixation test, and an insignificant degree of fixation found. The titer was approximately 16, whereas that of a negative control serum was 4 and a moderately high-titered serum was 128 in the same test.¹⁰

DISCUSSION

As has been indicated, very little autopsy material from cases of mumps has been adequately studied, and what changes have been described are not sufficiently specific for an etiologic diagnosis. So far as mumps myelitis is concerned, which more correctly is probably encephalomyelitis, the case reported above is probably the only one in which much detail is available, and even in this case the clinical history supplied the primary proof. Nevertheless, the histopathology of the parotid was similar to that described by Johnson and Goodpasture¹¹ in their experiments on monkeys. The changes in the brain and spinal cord were much like those previously described in the review by Donohue.⁵ The pathological changes in the lungs were not specific, but taken together give a picture like that described by Golden¹² in a review of 21 cases of atypical pneumonia. He noted the similar histopathological changes in pneumonia of influenza-virus etiology, of measles and of so-called atypical pneumonia, and grouped them as an acute interstitial pneumonitis. Incidentally, although Donohue's patient died of pulmonary involvement also, the report simply states "there were patchy and confluent areas of typical bronchopneumonia." In the literature on mumps there is no description of the disease in the lung such as that seen in our case.

The viral studies in this case apparently supply only negative results. It must be kept in mind, however, that certain viruses were excluded, and that failure to isolate mumps virus from the post-mortem tissues can have no bearing on the pathological diagnosis. In demyelinating meningoencephalitis one would not expect to isolate virus ordinarily. There was an interval of four days prior to inoculation, and this definitely reduces the chances of isolating mumps virus, which is labile. At the time the case was being studied, mumps virus could be readily isolated from saliva in the first two days of parotitis by inoculation of monkeys. In the meantime the virus has been isolated in eggs by Leymaster and Ward¹³ from the saliva of patients as late as six days after the onset of the disease.

In general, however, diagnostic dependence is placed upon the demonstration of complement-fixing antibodies. Although the blood on admission in the case reported above showed insignificant fixation, the patient's death precluded a subsequent sample, and it is regrettable that another blood specimen was not withdrawn at the time of death, for Enders¹⁴ has found that even in a week the antibodies may show a significant rise. But, in connection with complement fixation, new developments have come in the meantime. The



FIGURE 4. Section from the Lung, Showing Polymorphonuclear Exudate within the Bronchial Lumen, Sloughing of Bronchial Epithelium and Infiltration of Submucosa ($\times 115$)

The alveoli are relatively free of exudate, although scattered lymphocytes, mononuclears and plasma cells may be seen. The interstitial tissue also shows a mild infiltration by these cells.

adaptation of mumps virus to the chick embryo has revealed at least two serologically distinct complement-fixation antigens: the virus-bound or V antigen and the soluble or S antigen. The use of both antigens has permitted the early diagnosis of manifestations of mumps in the absence of parotitis, such as meningoencephalitis, since the finding of high levels of anti-S and of low or no titers of anti-V is considered diagnostically significant for the first few days of illness.¹⁵

There are only hypotheses concerning the cause of the central-nervous-system involvement of mumps

oriented. He could not sleep. The mucus became purulent. Death ensued on June 27.

Post-mortem examination, performed within 1 hour of death, revealed slight cyanosis of the ear lobes and lips. In the midline of the neck was a recent tracheotomy wound. There was swelling bilaterally in the region of the parotid gland, but the only abnormal gross finding was some edema of the gland itself and the surrounding tissue. Both lungs were somewhat heavier than normal, and both were deep purple and nonaerated, except for the upper portions of the upper lobes, which appeared normal. Most of the major

tis. The leptomeninges revealed some round-cell infiltration, insufficient to suggest an acute meningitis. Within the spinal cord there were early degenerative changes in the anterior-horn cells and marked perineuronal edema (Fig 2 and 3).

The pathological changes in the lungs consisted of an acute bronchitis and bronchiolitis, the lumens containing an exudate of leukocytes and the walls an infiltration of lymphocytes and mononuclear cells. The mucous membranes were partially necrotic. The alveoli were collapsed, but there was very little exudate within them. The cellular elements within the alveoli were predominantly lymphocytes and mononuclears, and there were also some of these within the alveolar walls (Fig 4). Cultures of the material within the bronchi yielded a few colonies of *Staphylococcus aureus*. Suctioned sputum obtained before death also yielded a few colonies of *Staph aureus*, and the direct smear showed many pus cells and an occasional gram-positive coccus.

Specimens of these tissues were also submitted to the head of the Department of Neurology at the University of Minnesota Medical School, who gave the following opinion:

The sections show minimal alterations. There are a few petechiae and some vascular congestion. The white matter demonstrates a mild diffuse gliosis and an occa-



FIGURE 2 Section from the Cerebral Cortex, Showing Longitudinal Section of a Small Vessel around Which There Is Some Demyelination and Lymphocytic Infiltration (x 800)

and minor bronchi were filled with a yellow, tenacious, elastic material, which was only moderately adherent to the bronchial walls. The bronchial mucosa showed some increase in vascularity. The pancreas and testes did not appear abnormal. The brain weighed 1330 gm and was marked by unusually prominent blood vessels. This increased vascularity also characterized the spinal cord. There was no gross evidence of exudate, although the spinal fluid was slightly cloudy. Portions of the brain and lungs were placed in 50 per cent glycerol for shipment to the state laboratory.

Microscopical examination demonstrated several areas of lymphocytic infiltration in the parotid gland. Some of the cells of the acini contained pyknotic nuclei, suggesting early necrosis, but for the most part the structure was well preserved. Numerous darkly stained areas were seen within the cytoplasm of the cells, these were tentatively identified as inclusion bodies, although their exact nature is not known (Fig 1).

The changes in the brain and spinal cord, although non-specific, were beyond question. Besides the diffuse dilatation of vessels, there was a mild perivascular demyelination and some proliferation of glial cells. Many vessels showed endothelial proliferation. The alterations were found primarily in the cortex and were indicative of encephali-



FIGURE 3 Section from the Anterior Horn of the Cervical Cord, Illustrating Marked Perineuronal Edema (x 480)

tion. A thin zone of perivascular myelin degeneration. The ganglion cells appear normal, however, a few within the brain stem show a few regressive changes. There is a mild endothelial proliferation in some of the cortical vessels. These changes are nonspecific but are suggestive of a mild encephalitic process.

Specimens of brain and lung in 50 per cent glycerol, received at the New York State laboratory on July 1, were used for inoculation of guinea pigs and mice in order to rule out the neurotropic viruses of the encephalitis group and

body or pulmonary neoplasm. Also, this may aid in better drainage and aeration of the diseased area. During bronchoscopy it may be feasible to aspirate the abscess cavity and to instill a suitable chemotherapeutic agent. Repeated bronchoscopic aspiration with instillation of penicillin directly into the abscess cavity as a form of definitive therapy has been widely used abroad but seems to be viewed with varying degrees of favor in the United States.^{3, 4, 7-9}

Adequate drainage of the abscess cavity is essential for successful medical treatment. One accomplishes postural drainage by inverting the patient with his head to the floor and with the body tilted so that the affected lung is uppermost. This should be done at least four times daily. Personal attention to determine the optimal position of the patient will frequently ensure good drainage when unsatisfactory results have been achieved previously. As a further aid to pulmonary drainage patients are taught to sleep without a pillow and with the foot of the bed elevated 20 to 30° during the course of therapy.

CHEMOTHERAPY

Multiple organisms are usually present, and abundant gram-negative organisms have been noted in the sputum after the administration of penicillin alone.¹⁰ For these reasons parenteral administration of both penicillin (50,000 to 100,000 units every three hours) and sulfadiazine or a mixture of sulfadiazine and sulfamerazine sufficient to maintain a blood level of approximately 12 mg per 100 cc is recommended. Local chemotherapy as penicillin aerosol, 40,000 units in 1 cc of isotonic sodium chloride, is administered with a vaponephrin nebulizer. A satisfactory aerosol spray is obtained by an oxygen flow of 5 to 7 liters per minute. A Y tube that diverts the air when the patient is not inhaling is used. No mechanism for condensing the expired air has been considered necessary. Aerosol therapy is carried out at four-hour intervals, preferably after postural drainage. In case organisms sensitive to streptomycin are isolated, streptomycin should be given in addition to penicillin both by aerosol and by the parenteral route. It has been suggested that the efficacy of aerosol can be enhanced by the addition of detergents such as agents of the quaternary ammonium series as zephiran chloride.¹¹ Such agents were not used in the cases reported below.

CASE REPORTS

CASE 1 A 35-year-old man was admitted to the respiratory ward of the hospital on February 22, 1947, with chills and fever that had followed recovery from a drunken stupor. The lung fields were clear, and he was treated symptomatically as a case of acute respiratory infection. At the end of 8 days the temperature was spiking daily to 104°F, and rales and consolidation were first noted in the right-upper-lung field. A roentgenogram of the chest revealed a wedge-shaped area

of consolidation to parenteral penicillin.^{10, 12} Some sur-
able radiolucent and the experience of seeing patients
consolidation. Sputum
hemolytic and green. S-
was given 50,000 units of penicillin in preparation for surgical
tion at 3-hour intervals. Because 3 cases reported above
dation numerous sputum specimens
fast bacilli, all were negative. The patient had
a febrile course, and 8 days after institution of
therapy a roentgenogram revealed an extensive
monic process, with a large central area of translu-
a questionable fluid level (Fig 1). He received
parenterally for 20 days, with no improvement. On
22 oral administration of sulfadiazine, penicillin aerosol, and
postural drainage were started. Within 5 days he became
afebrile, and a film of the chest showed diminished surrounding
reaction in the right-lateral-lung field and a definite abscess
cavity was no longer demonstrated. There was progressive
clearing of the lung fields, and only a small linear scar re-
mained. The sputum diminished and became negligible.
The sedimentation rate dropped from 50 mm to 4 mm per
hour (Wintrobe method). Therapy was continued for 6 weeks.
The patient was followed for an additional 2 months without
return of pulmonary symptoms or evidence of lung abscess
on repeated roentgenographic examinations.

CASE 2 A 42-year-old man was admitted to the hospital on April 13, 1947, with paroxysmal coughing and hemoptysis of 1 month's duration. The patient produced 500 cc. of pink, bloody sputum in 24 hours. His symptoms had begun 4 days after extraction of all his teeth under pentothal anesthesia. He had noted progressive dyspnea, pain in the right side of the chest and a weight loss of 17 lb. He was afebrile on admission. A roentgenogram of the chest revealed an abscess cavity in the right-lower-lung field. This cavity measured 4 by 5 cm in diameter and showed a fluid level (Fig 2). Bronchoscopic examination showed only inflammation in the right-lower-lobe bronchus. He was placed on the previously outlined course of therapy on April 16, and made a dramatic symptomatic and radiographic recovery. The daily sputum decreased from 500 cc. to 20 cc. within 2 days. Therapy was continued for a total of 24 days. Films of the chest taken 8 days after the institution of therapy showed disappearance of the previously seen abscess cavity. During the 24 days of therapy there was a rise in the hematocrit from 34 to 41 per cent. On completion of therapy the patient was discharged from the hospital without symptoms. He was followed for a period of 18 months, during which three roentgenographic examinations failed to reveal evidence of lung abscess and he had no pulmonary complaints.

CASE 3 A 26-year-old woman had had an infected molar extracted under local anesthesia on August 25, 1948. On August 30 fever and pleuritic pain in the left-lower-lung field developed. She was hospitalized 1 day later when the temperature was 101°F, the pulse 100, and the respirations 30. X-ray study of the chest revealed an area of increased density in the left lower lobe, with slight pleural thickening. The changes were considered indicative of pneumonia. The sputum was negative for hemolytic streptococci or pneumococci. The white-cell count was 12,000, with 85 per cent neutrophils. The patient was given 50,000 units of penicillin at 3-hour intervals and became afebrile and asymptomatic within 2 days. X-ray examination of the chest on September 7 showed slight clearing and she was discharged for follow-up study as an out-patient. Five days later she returned to the hospital with a recurrence of chills and fever. A film of the chest revealed an oval type of pneumonia in the area previously involved that was rather sharply circumscribed on the lateral film. This was again considered to be pneumonia although shut-off abscess or interlobar fluid was considered as a possible diagnosis. The temperature was 102.4°F, the pulse 110, and the respirations 26. Examination of the blood disclosed a white-cell count of 14,600, with 87 per cent neutrophils. Intramuscular administration of penicillin 50,000 units at 3-hour intervals, was started, with no improvement. Examinations of the sputum were negative for pneumococci, tuberculosis and hemolytic streptococci. The patient became progressively worse, the temperature spiking as high as 104.4°F, although she was receiving sulfadiazine in addition to penicillin. On September 17 she was placed in the head-down

and other common communicable diseases, and these are reviewed by Donohue⁵ and others^{2, 6, 16}

SUMMARY

A case of mumps myelitis with post-mortem studies, as well as viral studies, is presented, and the literature is briefly reviewed. This is probably the first case so fully reported. Symptoms and signs of myelitis preceded parotid swelling by three days. The pulmonary involvement, which was the cause of death, was consistent with viral disease, but whether it was caused by the primary virus is problematic. Newer diagnostic technics that were unavailable at the time the case was studied are discussed.

I am indebted to Dr. Max Newer, who had charge of the case, for permission to report it, to Drs. Alderman, Budgen, Rubenstein and Joseph Delmonico for consultation and assistance in handling various aspects of the case, to Dr. Irving Gordon, of the Division of Laboratories and Research, New York State Department of Health, for the viral studies, to Dr. Roemmelt and the Pathological Department of the Syracuse University College of Medicine for the autopsy and study of the sections, and to Dr. A. B. Baker, head of the Department of Neurology of the University of Minnesota Medical School for review of the sections.

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MEDICAL TREATMENT OF ACUTE PULMONARY ABSCESS*

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PLAN OF MEDICAL TREATMENT

Early diagnosis is most important. Lung abscess should be considered as a possible diagnosis in all "chronic" or "unresolved" pneumonias. Roentgenographic examination usually shows the characteristic area of pulmonary evacuation. A fluid level is generally present. However, about 5 per cent are shut off from bronchial drainage,⁵ do not manifest a fluid level and are difficult to differentiate from pneumonic infiltration. Lateral and oblique views are often needed for correct localization of the disease and to demonstrate lesions lying behind the heart. Identification of organisms in the sputum is important. However, multiple organisms are usually present, and in adults Smith⁶ has found anaerobic fusospirochetal organisms in 90 per cent of lung abscesses and believes these to be the principal etiologic agent. Abscesses secondary to pulmonary neoplasms, multiple embolic abscesses, primary bronchiectasis, tuberculosis and mycotic infections must be considered in the differential diagnosis and must be ruled out by appropriate studies.

Bronchoscopic examination is advised in all cases to establish the presence or absence of a foreign

IN TREATING patients with suppurative lung abscess the practitioner is often confused by the conflicting views expressed in current medical literature. Should such cases be treated surgically from the onset, with immediate drainage or resection,¹ or should they be followed with watchful expectancy because some will heal spontaneously?² It is my opinion that neither view is correct, that time is precious and that intensive and strenuous medical measures should be instituted immediately. If these procedures do not meet with rapid success, surgical intervention should not be delayed. When lung abscesses were diagnosed early, medical measures have led to recovery in as high as 80 to 90 per cent of cases.^{3, 4} When such methods do not result in cure they usually make the patient a better risk for surgical intervention. It is the purpose of this paper to outline in detail a proposed method of intensive medical therapy for acute lung abscess and to report 3 consecutive cases in which it has been successfully employed. Two of these were putrid lung abscesses, and the third appeared to be of the nonputrid post-pneumonic variety.

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justifiable to consider all pulmonary abscesses as surgical problems from the onset. Intensive, comprehensive medical therapy of acute lung abscess will effect a cure in the majority of cases. This should include not only systemic penicillin but also systemic

refractive to parenteral penicillin.^{10 12} Some surgeons have had the experience of seeing patients with lung abscesses recover while they were receiving penicillin aerosol in preparation for surgical treatment.^{10 11} Two of the 3 cases reported above

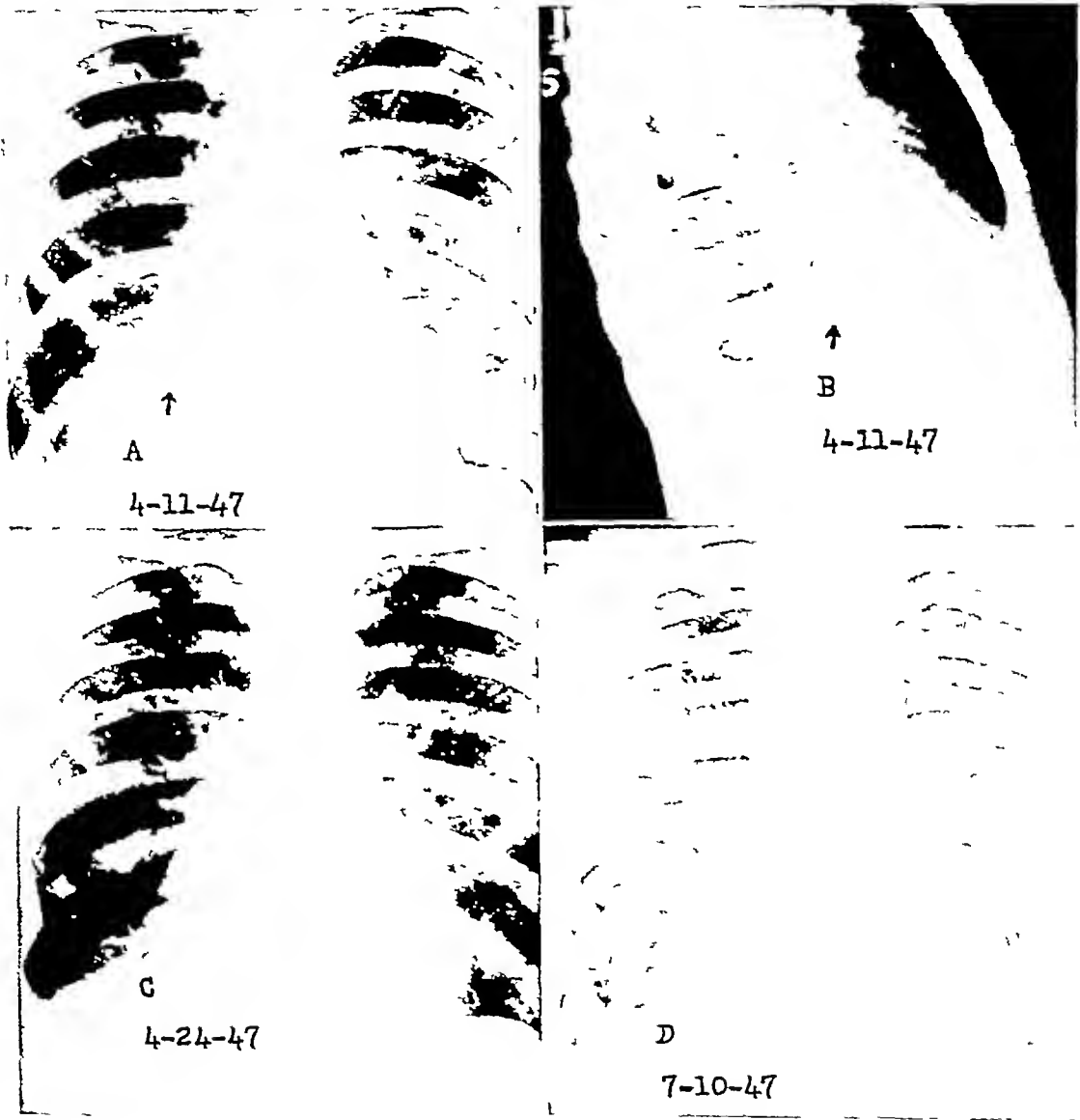


FIGURE 2 Case 2

A=chest film, demonstrating a large abscess cavity with a fluid level. B=right lateral view of the abscess cavity, showing the fluid level. C=film taken thirteen days later, after the abscess cavity is no longer evident. D=follow-up film taken two and a half months later — there is no evidence of pulmonary abscess.

sulfadiazine penicillin aerosol vigorous and frequent postural drainage bronchoscopic examination and the prompt use of streptomycin or other chemotherapeutic agents indicated. After penicillin aerosol therapy other authors have frequently noted recovery from pulmonary abscess in cases

failed to show improvement on parenteral administration of penicillin but healed almost immediately when a comprehensive course of therapy, including penicillin aerosol, was instituted. A shut-off abscess in which drainage through the bronchus cannot be accomplished is an indication for prompt sur-

and other common communicable diseases these are reviewed by Donohue⁶ and others.

SUMMARY

A case of mumps meningitis, as well as viral pneumonia, is reported. The literature is reviewed. This is the first case of mumps meningitis reported in the United States. Signs of mumps were present for three weeks. The patient was treated with penicillin and streptomycin. The patient continued to improve. The patient was discharged on October 9. After discharge from the hospital she was symptom free, and films of the chest 1 and 5 months later were clear.

—WALKER

wed progressive diminution in size. On October 1 it could no longer be demonstrated. Therapy was continued until October 9. After discharge from the hospital she was symptom free, and films of the chest 1 and 5 months later were clear.

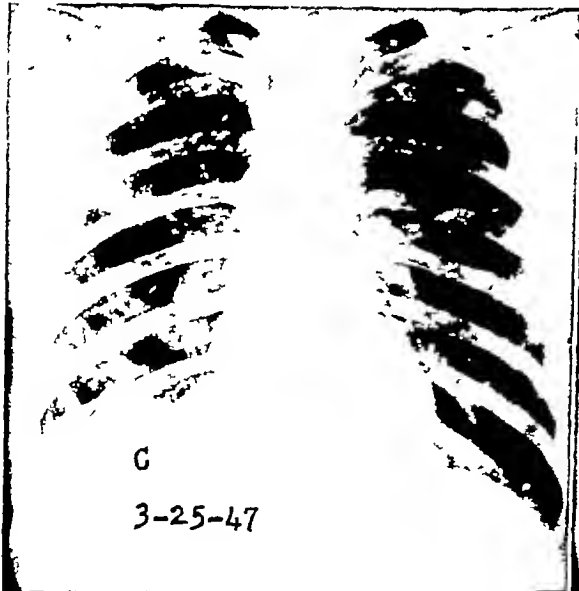
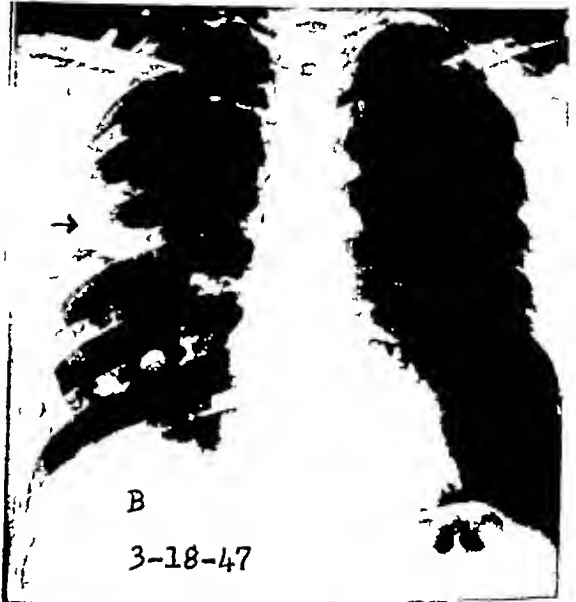


FIGURE 1 Case 1

A=extensive pneumonia of the right lung, with an area of rarefaction suggestive of pulmonary abscess. B=overexposed film taken eight days later, demonstrating a pulmonary abscess with a fluid level. C=abscess cavity is no longer apparent, and there is beginning linear scar formation. D=follow-up film one and a half months later, showing residual linear scar. (All roentgenograms were reproduced by Madigan General Hospital Photographic Laboratory, Tacoma, Washington.)

choscopy, with essentially negative findings, 100,000 units of penicillin and 0.5 gm. of streptomycin in 5 cc. of isotonic sodium chloride were instilled into the left-lower-lobe bronchus. After this procedure she was started on a course of postural drainage and penicillin aerosol in addition to the systemic penicillin and sulfadiazine she was already receiving. She became afebrile within 2 days, and the abscess cavity

DISCUSSION

Since some authors have reported cure rates as high as 90 per cent^{3, 4} from the medical treatment of acute pulmonary abscess, it is no longer thought

MEDICAL PROGRESS

PSYCHIATRY

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IT IS gratifying to psychiatrists to see the importance of their specialty more and more clearly recognized and understood by medicine generally and by the public. The situation beginning with and since the war suggests that psychiatry may be approaching its heyday. The hope should be that its structure is or will be on foundations so sound that as time goes on it will not suffer through periods of questionable repute.

Even at present, it may be considered, a little uneasy, if there are signs of excessive enthusiasm or fervor in some directions. In speaking of the ominously revolutionary trends of today's social forces, Chisholm¹ says, "Without the extensive help of psychologists and psychiatrists it is quite probable that mankind will not long survive the fearful changes which are taking place." Perhaps this statement was calculatedly exhortative for the psychologists and psychiatrists, but if it was seriously meant for just what it says it seems wise for those addressed to decline modestly the honor of saving the race.

There is no evidence psychiatric or sociologic, that psychiatry has or can have the power and influence to shape man's course in the universe. Gregg,² to whom psychiatrists seem to listen with respect, writes, "Psychiatry can wave no magic wand and so obliterate powerful social forces and the conflicts that accompany enormously complicated social transitions, even if it has been fondly hoped or vaingloriously imputed to have such powers." Gregg's whole paper is an excellent, sympathetic evaluation of the place, possibilities and limitations of psychiatry. In an article written some time back, cautioning against unwarranted expectations from psychiatric treatment, the following remarks were made:

Reflecting on the frailties of human nature, one may well wonder whether religion or science presents the better road toward a better race. Psychiatry should play its part best by holding to a steady course in which it does not permit itself acclaim beyond its actual accomplishments.³

A more far-reaching development in psychiatry than any possible tendency toward assuming omnipotent capacities, a development that should be regarded more critically and objectively than it is in some quarters, is the body of Freudian psychoanalytic concepts. Today, psychoanalytic terms are so tossed about that the layman is likely to

assume that, in using them, he is referring to established truths, and even some psychiatrists are timid about challenging their authenticity, thinking that they as professional men may not be so well informed as they should be.

The valid accomplishments of psychoanalysis should not be discredited but psychiatry and people generally should not accept theoretic formulations and part-truths as scientific facts or whole truth. Menninger⁴ has written, "Actually, sex is the basic and all-pervasive motivation in life, and it must be understood for a healthy mentality." In reality, it has yet to be proved in regard to unmeasurable motivation that sex is any more basic than the forces or drives of self-preservation and self-development. To pronounce that sex alone is basic is to interpret human behavior in such manner as to substantiate a theory that one may want to believe but that is not supported by facts as we know them.

One may ask what difference it really makes whether or not sex, even in the broad, inclusive sense meant by psychoanalysis is considered the basic motivation. The importance of this is that the so-called interpretive or dynamic evolution in psychiatry has, by a number of causes, gained, assumed and maintains to an influential degree an authoritative position to which it is not entitled on scientific grounds. If psychoanalysis designates itself as a church, as a system of ideas and beliefs, that helps people to live more contentedly, more constructively, there is no quarrel between it and science, unless science itself has become headstrong.

To delineate further the authoritative position Menninger⁵ writes, "The misdirection of the aggressive drive is the basic cause of all maladjustment," and "The psychiatrist is convinced that emotional maturity can be reached only through a childhood experience in a situation that provides affection, good example, and security," and "Psychiatrists uniformly agree that the great majority of psychological cripples receive the injuries that predispose them to their crippled state in childhood, very often even in infancy."

Psychiatrists, if they have been well educated, and if they have not forgotten their education and if they retain the scientific attitude do not agree with such sweeping statements. They know there is little about which they can be sure, and they do

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gical intervention. It is my belief that cases with satisfactory drainage that fail to show regression within four weeks should be treated surgically if repeated bacteriologic studies do not show organisms that require the use of additional chemotherapeutic agents.

Early diagnosis is the most important factor in determining the number of cases that will be cured by medical means. Few cures have resulted from medical treatment in chronic lung abscesses.⁶ These cases should ordinarily be treated by resection of the involved lung.^{13, 14} However, preoperative therapy similar to the treatment outlined for acute lung abscesses will result in improved preoperative condition of these patients and in an occasional medical cure. I agree with Scannell's¹⁵ suggestion that the therapy of lung abscess may largely resolve itself into a decision between medical treatment and extirpation.

Rubin¹⁶ has pointed out the most frequent cause of lung abscess to be an operative procedure on the oropharynx. Most observers believe putrid pulmonary abscess formation is due to aspiration of infected material, which lodges in a sublobar bronchus, producing a severe acute necrotizing inflammation. These are usually associated with chronic gingival infections.⁶ One of my cases followed multiple tooth extractions under general anesthesia, and another followed tooth extraction under local anesthesia. In both cases extractions were performed because of perialveolar abscess. There was no evidence that a particle of tooth had been aspirated in either case.

Postural drainage is a strenuous procedure and should be used with caution in the presence of cardiac disease or threatened pulmonary edema. However, it is undoubtedly one of the most important single therapeutic agents employed. The only complication from postural drainage in these cases was a small conjunctival hemorrhage.

SUMMARY AND CONCLUSIONS

It is proposed that a comprehensive plan for the medical treatment of acute pulmonary abscess should include both systemic penicillin and sulfadiazine, penicillin aerosol, adequate postural drain-

age, bronchoscopic examination and the prompt use of streptomycin or other chemotherapeutic agents indicated by bacteriologic study.

Three consecutive cases of acute pulmonary abscess were successfully treated in this manner. Two were putrid lung abscesses, and the third was of the nonputrid post-pneumonic variety. All cases showed complete disappearance of abscess cavity by roentgenographic examination within fourteen days of the institution of the therapy outlined. Two of the 3 patients had previously failed to improve under treatment for six and twenty days, respectively, with parenteral administration of penicillin.

It is believed that all suppurative lung abscesses, except for those shut off from bronchial communication, should receive such initial treatment with the expectation of cure in the majority of acute abscesses and better preparation of the chronic ones for pulmonary resection.

The view that all lung abscesses are surgical problems from the onset should be modified.

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tility is present with no relation to the analyst or his attitudes there is still no reason to assume that it is a basic quality in the patient's personality or in the symptomatic configuration

In a magazine article Alexander¹³ refers to the two world wars and concurrent tyranny and cruelty as confirming "Freud's contention that behind a veneer of civilization man hides an asocial nucleus more destructive than the atomic nucleus he recently put to such devastating use." By "asocial nucleus" Alexander means an inborn destructive impulse or instinct, according to the context. Here again is an example of making the facts fit the theory—perhaps, to use the Freudian term, an example of repetition compulsion. To submit the chronologic and sociologic facts that two world wars have occurred within the past thirty-odd years, the fact that man tortures and persecutes man and the fact that man now has contrived a machine that could conceivably effect his own destruction—to present these facts as proof of an inborn impulse for destruction might connote superficial intelligence unless it is remembered that brilliant minds can be subject to circular or orbital thinking.

There is no proof whatever that, in either world war, men *generally* fought, destroyed, killed and maimed because of any deep impulse or drive—under the circumstances permissible or legalized—to do so. One might almost say that anyone knows that men fought because they had to, because their governments ordered them to and because of the consequences, personal and national, if they didn't. No doubt some men, some of the Germans, for example, in the recent war, zealously wanted to fight and had to make no effort to supplant any other primary desire, because they were so purely imbued with or indoctrinated in the master race ideology. We know that some men at least a few, earnestly desired to be "in it" because they did not want their "way of life," the democratic ideal, to be replaced by more palpable at least, tyranny or dictatorship. Also, no doubt, many men, gradually or latterly, became enthusiastic, more or less, because they did not want their way of life in practical obvious ways, to be changed for a probably indefinite period.

Most people are not particularly reflective, and therefore it may be reasonable to assume that the great majority of men who participated in the two world wars did so because they immediately thought there was no choice but to do so or because they were swept along by social forces that they did not actively oppose.

However, since men did as they did—destroyed, killed, caused untold anguish—it is asserted that they did so whether or not they consciously knew it, because they were impelled by one of two exclusively basic motivations. Except for those who would not be suitable for psychoanalysis, if all the people who took part in the world wars and all those

who did not take part, some professedly on principle, were to be psychoanalyzed—including in this number the rather timid man in a civilian-defense unit who was never confidently sure just how to apply the Thomas splint, and the many men and women who were considered unfit for active combat—successful analysis would reveal to the analyst and analyst that each individual was in it or not in it because he was motivated by a powerful instinct for destruction that, by most individuals, had not been consciously recognized or admitted.

If the presence and import of this instinct were not revealed by and to the analyst after an indeterminate lapse of time, resistance would still be obstructive, transference would not have been effected, the subject would be found unsatisfactory for analysis or the investigation would have to be terminated because of financial considerations.

It is submitted that a more credible explanation for the chaos that man creates for himself is a drive or motivation deeper and more pervasive than a supposed instinct for destruction. This force may be called self-interest. Most of the troubles into which man, singly and collectively, gets himself can be traced back to self-interest as a basic cause. From it can arise unlimited desire for power and acquiescence, and from its frustration can develop interpersonal animosity, hate, cruelty. On a larger scale, groups can be ruthless with each other, even to the extreme of employing atomic bombs, not primarily because of a desire to destroy but from a desire either to protect their interests or to increase their influence. Self-interest or self-protection, unfortunately and tragically for human welfare, is shortsighted and unenlightened, and there are few men who can think and feel beyond it if their particular Achilles heels have been hit. It might be called the greatest and too nearly universal human obsession. Its egotistic needs, cravings and demands are so powerful, subtle, devious and unrelenting—sometimes shrewdly calculating or compromising, consciously or unconsciously, and at other times catastrophically blundering for the individual—that it could conceivably propel to man's extinction. There is little wonder that Christianity considers it an important element in the doctrine of original sin.

The unsubstantiated theory of instinctive aggression or self-destruction serves self-interest neatly and subordinately. If the theory is accepted unquestioningly as fact, the acceptor is likely to excuse and exonerate himself for any hostility or hatred on the basis that, in all fairness, he can hardly be asked or required to oppose successfully in thought or action a force as intrinsic as the action of his heart. He may even get to thinking that it is not only all right but healthy to exhibit hostility. However, this is not the place for a disquisition on the theory of self-interest and self-protection.

not overlook or discard the importance of constitution and heredity in human behavior

In a critical essay on what he calls "autistic trends in psychiatric thinking," Freyhan⁶ nicely analyses the dangers of overemphasis on the dynamic interpretation of psychiatric or personality disorders

Positivistic ideologies have produced a tendency either to underestimate or even to ignore the necessity of appraising constitutional and hereditary aspects of psychiatry. It is hardly an exaggeration to state that these factors are actually taboo in general psychiatric discussions. The often heard argument that investigations in these fields have failed to yield tangible results is not in accord with facts and must be regarded as another symptom of autistic rationalization

Farther along, he states "Bartemeier stressed the importance which Freud attributed to the hereditary predisposition and warned that one-sided preoccupation with environmental factors is not at all in accordance with Freud's total theory of psychopathogenesis." Freyhan's paper is worth reading in its entirety by anyone who may wonder if he has become a little unbalanced on the subject of psychiatric etiology

It may be recalled that Freud⁷ himself stated his position as follows

The expectation that we shall be able to cure all neurotic symptoms is, I suspect, derived from the lay belief that neuroses are entirely superfluous things which have no right whatever to exist. As a matter of fact they are serious, constitutionally determined affections, which are seldom restricted to a few outbreaks, but make themselves felt as a rule over long periods of life, or even throughout its entire extent. Our analytic experience that we can influence them to a far-reaching degree, if we can get hold of the historical precipitating causes and the incidental accessory factors, has made us neglect the constitutional factor in our therapeutic practice. And we are in fact powerless to deal with it, but in our theory we ought always to bear it in mind. In any case, the complete inaccessibility of the psychoses to analytic therapy should, in view of their close relationship to the neuroses, moderate our optimism in regard to the latter. The therapeutic efficiency of psychoanalysis is limited by a whole series of important factors, which can scarcely be dealt with at all

Psychoanalysis may demur, saying that, even in post-Freudian development, it makes no assertion that it effects cures in whatever problems it undertakes, that it is essentially an investigative discipline and as such is interested in disclosing the fundamental structure of psychopathology. Undoubtedly the interest in psychopathology is genuine, but there is an inclination to make too wide application of theoretic psychologic or psychobiologic nuclei, sets, complexes or so-called instinctive drives. One example is the maintaining that in a large percentage of cases of alcoholism an etiologic factor is a latent or conscious homosexual conflict. Another is the assumption that the same conflict is etiologically present in the paranoid states. One paper, suggesting that healthy, scientific doubt and objectivity are not swamped, is the report of a study, by Klein and Horowitz,⁸ of 80 patients who had diagnoses of paranoid state

or schizophrenia, paranoid type. These writers conclude

The paranoid mechanism cannot be explained solely by homosexual conflict despite the convincing evidence of its pertinence in certain cases. It is so obvious in the cases in which it occurs, that the limits of its application are all the more surprising. If the relationship of homosexuality to the paranoid mechanism is assumed to be invariable, other important considerations will be neglected

The actual existence in human nature of an inherent, instinctive drive of destructiveness or aggressiveness, expressed by hostility toward various parts of the environment, is too much taken for granted by some psychiatrists. Freud⁹ wrote, "The bit of truth behind all this — one so eagerly denied — is that men are not gentle, friendly creatures wishing for love, who simply defend themselves if they are attacked, but that a powerful measure of desire for aggression has to be reckoned as part of their instinctual endowment." Horney¹⁰ quotes Freud as saying, "Hatred is at the bottom of all the relations of affection and love between human beings."

Not all investigators agree that an instinct of aggression is an essential part of the warp and woof of our structure. Horney¹⁰ says, "The theory of a destruction instinct is not only unsubstantiated, not only contradictory to facts, but is positively harmful in its implications." She sees aggression and hostility as reactions provoked by frustration

If we want to injure or to kill, we do so because we are or feel endangered, humiliated, abused, because we are or feel rejected and treated unjustly, because we are or feel interfered with in wishes which are of vital importance to us. That is, if we wish to destroy, it is in order to defend our safety or our happiness or what appears to us as such. Generally speaking, it is for the sake of life and not for the sake of destruction

From her comprehensive experience with children, Bender¹¹ is not able to accept the Freudian theories of aggression and hostility. She thinks this emphasis is one-sided and "has led our students of child psychology astray." She believes "the child has an inherent capacity or drive for normality" and "that aggression in childhood is a symptom complex resulting from deprivations which are caused by developmental discrepancies in the total personality structure such that the constructive patterned drives for action in the child find inadequate means of satisfaction and result in amplification or disorganization of the drives into hostile or destructive aggression."

That psychiatrists, like other people, may get what they are looking for is suggested by Johnson,¹² in his critique of psychoanalysis. He contends that "free" association, in the analytic procedure, is not really free, that the patient is influenced by the analyst's conceptions and ideational systems. I propose, somewhat comparably, that if the analyst is looking for hostility or evidence of aggression for example, he, by his own attitude, may easily create it or augment it in the patient. Even if hos-

his system may carry a hallmark of truth that is not merited. An impressive example of this is the extent to which the concept of the Oedipus complex has made a place in psychiatric and common thought.

Sears,¹⁶ in a report of objective investigations of psychoanalytic concepts, writes, "Freud assumed the Oedipus relationship to exist universally, and while other investigators have found instances of it, no indications of a universal cross-sex parental preference have been discovered in either children or adults." The universality of this complex had previously been refuted by Westermarck¹⁷ for those who had ears to hear and eyes to see.

The same propensity for generalization occurs in relation to various other Freudian concepts. Again, Sears¹⁶ remarks

Several sources of evidence indicate, however, that Freud seriously overestimated the frequency of the castration complex and the importance of childhood sex aggressions. The castration complex, like theories of the origin of babies, is a function of the kinds of information children have. Freud's tendency to rely on cultural universals—which do not exist—has led him to postulate universal attitudes and complexes that can be demonstrated in but a part of the population.

A dominant defect of the Freudian psychoanalytic discipline is to take or mistake a part for the whole, unwarrantedly to assert that a complex or a number of complexes, which may or may not be present, are causative in human behavior.

With no depreciation of the significant work done by psychoanalysis, Sears¹⁶ concludes

The experiments and observations examined in this report stand testimony that few investigators feel free to accept Freud's statements at face value. The reason lies in the same factor that makes psychoanalysis a bad science—its method. Psychoanalysis relies upon techniques that do not admit of the repetition of observation, that have no self-evident or denotative validity, and that are tinctured to an unknown degree with the observer's own suggestions. These difficulties may not seriously interfere with therapy, but when the method is used for uncovering psychological facts that are required to have objective validity it simply fails.

This does not mean that all psychoanalytic findings are false, but it does mean that other methods must be sought for their critical evaluation and validation.

The purpose of psychotherapy, including psychoanalytic therapy, is to relieve, as far as possible, the person from burdensome and handicapping behavior or thinking that prevents him from being reasonably contented. This would supposedly mean enabling the patient to get along better not only with himself but also with others. It is an almost everyday truism that the two most essential ingredients of this prescription are forbearance and tolerance, being more patient with and understanding of oneself and others, with various qualifications. In therapy, psychoanalysis surely would not state that it is interested only in the individual and has no concern with interpersonal relationships, for the two are interwoven and inseparable. If tolerance, forbearance and consideration for the other person

are essential, analytic therapy must be, or should be, working toward a fairly close semblance of the Christian meaning of love.

In a recent radio broadcast (Town Meeting, on April 26), Karl Menninger, the co-author of *Love Against Hate*, concluded that we should love rather than hate. A previous reference in this paper alluded to another authority,¹⁸ although not a scientist, who said much the same thing some years ago. If psychoanalysis, in its endeavors, finds reason to emphasize what Christianity has been advocating for centuries it seems that it and religion are not so disparate as some have feared. However, it should be said that to date there is no evidence that students, professors or advocates of psychoanalysis or persons who have gone through the expensive, time-consuming, analytic treatment are any more forbearing, considerate or loving of their fellow men than other people.

Earlier in this paper there was reference to the importance of constitutional and hereditary determinants in psychiatric illness. In discussing psychosomatic states, Freyhan¹⁹ again emphasizes that these constituents should not be disregarded. He writes that some psychiatrists, with their interest in psychogenic factors, seem to forget that the somatic side of the alliance exists. This could be thought odd if the very name of the partnership is kept in mind. Freyhan says, "We are told again and again that it is the conflict between powerful dependent needs and the aggressive solution of this conflict in the face of frustration of the receiving tendencies which is of crucial importance for the development of peptic ulcers." The sentence construction is somewhat confused, but the meaning is clear enough. He continues

Psychosomatic thinking can neither be based on well meant sociologic platitudes nor on outdated analytical concepts.

Unfortunately most psychiatrists pay little attention to modern genetic and constitutional researches, in fact the term "constitution" is practically taboo and still associated with therapeutic nihilism and reactionary organic-mindedness.

Daniels²⁰ gives a nod to the somatic side but apparently thinks the psycho more important. To quote him

One of the misconceptions in connection with the inclusion of psychic factors in the causation of physical disease is that these factors are made to represent "the whole reason" for the condition. Such an impression may arise from the overenthusiasm of the investigator or the misinterpretation of the critics.

The personality of these patients is vulnerable because of the persistence of emotional immaturities with marked inner dependence on a parental figure, generally the mother.

Somewhat belatedly Alexander²¹ allows a place for heredity in neurotic development. He writes

At the beginning of the Freudian era the importance of childhood experiences was discovered and claimed as the cause of neurosis. Gradually we have come to recognize at least three sets of factors which together in varying de-

As indicated previously, psychiatrists should be concerned with the trend in professional and popular thinking that allows some psychoanalysts, under the formidable aegis of Freud's power, and, in turn, many laymen to believe that they have an indisputable grasp of the truth. Any prominent, articulate physician, in expressing his opinions, may have a subtle or direct influence, which may be understood as signifying authority. In a recent review of Freud's last, posthumous book, *An Outline of Psychoanalysis*, Binger¹⁴ writes, referring to what Freud has written, "Here is the truth, he says, in effect — my truth — take it or leave it." Then Binger continues

By and large, modern, educated, Western men and women have chosen to take it. They either deny it with passion and vehemence, thereby, in a sense, acknowledging its threat, or they accept it. But they seldom understand it. In spite of clichés about "complexes," "fixations" and all the rest, they seldom comprehend the deep metaphysical and moral implications, the epic and heroic portrayal of life as a titanic struggle between two instincts — Love and Death.

At least to me, Binger implies that Freud was probably right. When he suggests that people who do not agree with Freud's truth may be acknowledging its threat, the implication seems to be that opposition to an idea weighs in favor of the rightness of the idea — that people rarely oppose untruth. Although it may be presumed that, in general, people do not like to face facts if they hurt personally, it also may be presumed that some people do not like to accept as fact ideas or pronouncements that are not supported by irrefutable or probably irrefutable data. Surely there are scientists who, without passion or vehemence, find no reason to accept Freud's dictums. Parenthetically, I happen to know some analysts who, with passion and vehemence, defend Freudian dictums. If by "threat," Binger did not mean "truth" or what is probable, but had in mind the dictionary definition, "an expression of an intention to inflict evil or injury to another," it may not be singularly aberrant of some Western men and women to deny Freud's truth.

Again, in stating that although, by and large, modern, educated Western men and women have accepted Freud's explanation, they "seldom comprehend the deep metaphysical and moral implications," Binger seems to be producing overtones, at least, of reverence, of awesome respect for Freud's ideas, if not for the man himself. Binger is aware of Freud's intransigence, and Freud¹⁵ leaves no doubt about it, with his introductory statement, "The teachings of psychoanalysis are based upon an incalculable number of observations and experiences, and no one who has not repeated those observations upon himself or upon others is in a position to arrive at an independent judgment of it."

"Deep metaphysical and moral implications" of various theories of man's whence and whither have been considered by poets, philosophers and

schoolboys ever since man became reflective. To give uncritical credence to Freud's theories is — to borrow phraseology from Winston Churchill* — something "up with which" scientists should not put

Psychiatrists know, or should know, that suggestibility is a characteristic of the human species, not excluding themselves. Through the ages men of forceful personality have influenced thousands of people to believe in them and in the rightness of their ideas. In our own time the phenomenon of Hitler can scarcely be overlooked.

As quoted above, Freud said, "Hatred is at the bottom of all the relations of affection and love between human beings." In analyzing the Christian commandment, "Thou shalt love thy neighbour as thyself," Freud⁹ has written

We will adopt a naïve attitude towards it, as if we were meeting it for the first time. Thereupon we find ourselves unable to suppress a feeling of astonishment, as at something unnatural. Why should we do this? What good is it to us? Above all, how can we do such a thing? How could it possibly be done? If the high-sounding ordinance had run, "Love thy neighbor as thy neighbor loves thee," I should not take objection to it. And there is a second commandment that seems to me even more incomprehensible, and arouses still stronger opposition in me. It is "Love thine enemies." I imagine now I hear a voice gravely adjuring me "Just because thy neighbour is not worthy of thy love, is probably full of enmity towards thee, thou shouldst love him as thyself." I then perceive the case to be like that of *Credo quia absurdum*.

This is very enlightening. A man who found hate behind all human affection and who found incomprehensible the import of loving one's neighbor as oneself, and who thought it absurd to believe that a man can love his enemies, is looked upon as having new and surpassing powers for penetrating personality. Probably Freud had such powers in some respects, but the powers were surely limited if he did not know and understand that there have been some men who loved and that there are some men who do love their enemies. Apparently it was not included in Freud's gifts of insight and analysis to conceive this kind of love. It seems to be a likely hypothesis that within Freud's own make-up there was a large measure of hatred, which led him to find the same quality in his patients.

This emphasis is of serious intent and does not spring from a carping or retributive attitude. The sway of Freud and his followers is great. Scientific, psychiatric progress is and will be impeded unless psychiatrists, more generally than at present, try to hold to an objective evaluation of their observations, beyond personal interest. If the founder of psychoanalysis is accepted and applauded as an incontrovertible authority, any ideas that he propounded and any ideas that are proposed under

*Winston Churchill had submitted a draft of an important wartime speech to the British Foreign Office for comment. The draft was returned with no comment whatever on content, but where he had ended a sentence with a preposition a Foreign Office purist had cared the preposition into its stuffy grammatical position. At this the Prime Minister flew into a lather. To the offending purist he despatched a note, "This is the type of agent p. lantry," read the note, "up with which I will no put!" (*Reader's Digest*, May 1949).

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CASE 35331

PRESENTATION OF CASE

First admission A fifty-one-year-old salesman was admitted to the hospital because of a cough productive of blood-streaked sputum.

He had been in good health until three months prior to admission when he first noticed streaks of bright-red blood in his sputum upon coughing. These episodes occurred about every other day for a week and then cleared. One week later he had another bout of hemorrhage that seemed to come from the mouth and nose and lasted ten minutes. Since that time he had had a number of episodes of coughing with blood-streaked sputum, unrelated to any particular activity. The patient stated that he had had a chronic cough for many years, usually associated with smoking. He denied a recent change in the character of the cough or any increase in the amount of sputum. He had lost 15 pounds in weight during the year prior to admission but had regained 10 pounds in the three-month period before coming to the hospital. One evening four months before entry, he had a chill and vomited some dark material. Later that night he awoke with pains in the mid-back. He had no cough or hemoptysis at this time, however, and felt well the next morning. Two weeks later an abscessed tooth was removed under a local anesthetic. The patient stated that for two months before admission he had noticed that one artificial tooth was missing. During the month prior to entry he had mild pain in the right arm and shoulder when he raised his arm to put on his coat. There was no history of wheezing, dyspnea, cyanosis or further chills. His appetite was good.

The past history was otherwise noncontributory except for a tonsillectomy and an attack of "rheumatism" thirty-six and twenty-eight years before, respectively. Seven years before admission the patient was taken into the Army for a nine-month

period. His father and a brother had died of tuberculosis some thirty-five years before.

Physical examination revealed a well developed and nourished man in no acute distress. The heart and lungs were normal, and aside from a small 1-cm cyst under the right eyelid, no abnormalities were recognized.

The temperature, pulse and respirations were normal.

The urine was normal. Examination of the blood showed a hemoglobin of 14.4 gm and a white-cell count of 9400, with 56 per cent neutrophils, 35 per cent lymphocytes, 3 per cent monocytes and 6 per cent eosinophils.

A roentgenogram of the chest showed a patchy area of increased density in the superior segment of the right lower lobe extending from the hilus to the pleural surface laterally and posteriorly. Above the area of increased density was an area of normal density surrounded by a thin rim of increased density. This was thought possibly to be a chance crossing of vascular shadows or a very thin-walled cavity. No foreign bodies were recognized.

Bronchoscopy was negative except for slight reddening of the right main bronchial tree. A cytologic smear of the sputum was negative.

In the hospital the patient's condition remained unchanged. A second history taken five days after admission established a different chronology to the points of progress of his disease as follows: an episode of grippe or cold four months before admission; a tooth extraction two weeks later; a dental plate inserted one week later and his first bout of hemoptysis some time thereafter. Three separate examinations of the sputum failed to reveal acid-fast bacilli. A culture of the sputum grew out abundant alpha-hemolytic streptococci and a few beta-hemolytic streptococci.

It was believed that the lesion in the right lower lobe was probably an abscess, and the patient was discharged on the sixth hospital day.

Second admission (about eleven weeks later) In the interval the patient had been well and free of hemoptysis until ten days before entry when he again coughed up small amounts of blood-streaked sputum. At this time, he also noted a temperature of 101°F, excessive sweating and a pleuritic type of pain in the lower portion of the right chest. The pain disappeared after two days.

The findings on physical and laboratory examination were essentially unchanged. A roentgenogram of the chest showed the density in the right lower lobe to be somewhat larger and its margin less distinct than on the previous study. There were also linear markings of increased prominence extending from the abnormal density to the hilus. There was a small fluid level within the density. There was a questionable small amount of fluid within the right pleural cavity.

gress contribute to neurotic disease. These factors are heredity, early experiences of life, and actual difficulties. A patient with poor hereditary equipment may be destined to develop neurosis no matter what happens to him.

Recognition of other factors besides early life experiences may have come gradually to some of the analysts, but they have been considered as possibilities and probabilities by many psychiatrists long before some groups of psychoanalysts admitted their possibly determining presence. If analysis takes credit for discovering hereditary, constitutional and immediately present difficulties in the patient's life situation as elements to be assessed in neurotic reactions, it gives itself the position of arbiter in psychiatry, which position actually it does not hold.

In the paper previously cited, Gregg² makes several references to the subject of heredity. He writes, "Until the medical profession sees its patients as having genetic as well as psychological and somatic histories we shall have to admit our professional ignorance of heredity and the only fragmentary knowledge as yet revealed as one of the primary remediable limitations of psychiatry." He says further, "Because among human beings an observer seldom can expect to outlive both the child and the child of the child he observes, the hereditary factors affecting mental defect, disease, or disorder and the components of personality, temperament, and patterns of behavior have received but little of the attention they deserve."

Gregg concludes, "Though it is still early to know how to think about human heredity there are few subjects more potent for the prevention of psychiatric defect, disorder, and susceptibility to strain. I cannot escape the conviction that we must begin to seek the way to find the truths of human inheritance."

No psychiatrist with therapeutic sense and sensibility will find his interest in or enthusiasm for

therapy dampened because of therapeutic limitations. In spite of its tragedies, psychiatry has, beyond estimable measure, mitigated human suffering. Until man, through religion or science, is reborn, psychiatry should hold a contributory and honored province and it will hold it best through a becoming admixture of humility.

330 Dartmouth Street

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On the eighth hospital day an operation was performed

DIFFERENTIAL DIAGNOSIS

DR CARROLL C MILLER The history of this case, the presumptive diagnosis and the subsequent surgical disposition seem to revolve around three salient features hemoptysis, signs and symptoms of pulmonary infection and x-ray findings in the right lower lobe. The causes of hemoptysis in the lower respiratory tract, in a broad sense, may be classified as follows for a brief review foreign body, with or without subsequent necrosis, infections, with necrosis and erosion of blood vessels (and most important, among these infections, are abscess, bronchiectasis, pneumonia or pneumonitis and tuberculosis), tumors, either benign or malignant, primary or metastatic—the latter rarely cause or produce hemoptysis, infarct, and finally heart disease and congenital anomalies of the vascular tree

In view of the x-ray findings in this case many of these can be omitted from discussion. Recurrent hemoptysis seems to direct our consideration into certain definite channels. Intermittence of hemoptysis is not uncommon, especially in tumors or infectious processes, since the growth of tissue in a tumor or the alternate necrosis and focal thrombosis associated with infection may account for freedom from bleeding for varying periods

This man had no previous history of any trouble in his lungs as far as we know, but he did have probable exposure to tuberculosis, since his father and a brother had died of tuberculosis many years previously. This fact may or may not have a bearing on the diagnosis

I was prompted to wonder why he spent such a short time in the Army, nine months, according to the record, in about 1942. But no explanation is given for that

He had had marked weight change—he lost 15 pounds in the year before admission, but this was before he became ill. During the period when his symptoms and signs were developing he had regained 10 pounds of that weight loss. So these details do not contribute in any definite way to the making of a diagnosis

The significant data in the history are that four months before his first admission he had an episode of chills and vomiting, two weeks later, a tooth extraction was done, and then the fitting of a dental plate, and, curiously enough, two months prior to admission he noticed that one of the artificial teeth was missing. This might be called the saga of the missing tooth. Following this episode he began to have blood streaks in his sputum. There are some details that I have tended to pass over. The arm and shoulder pain seem to have had no striking relation to the present illness. They may very well have been bursitis or tendinitis or some

recrudescence of rheumatism of many years past. The absence of wheezing noted in the protocol is important in indicating no significant obstruction to the bronchial tree. The culture as reported is not of importance. We have been tending in recent years to put less and less stress on sputum culture reports in conditions such as this, because, invariably, there is a mixed infection and only when we are interested in outlining a plan of antibiotic therapy are we interested in knowing exactly what the organisms are. In other words, in cases such as this with a relatively small, limited focus, the bacteriology does not significantly contribute to the making of a diagnosis except of course in the presence of tuberculosis

In recapitulation, therefore, we have an episode of infection, chill and mid-back pain and then later hemoptysis. X-ray studies at that time showed segmental density with a question of cavity in this area. The location of this cavity is emphasized in the protocol with the description of an area of normal density surrounded by a thin rim of increased density. This is above the segmental density noted to be in the superior segment of the right lower lobe. Then the patient had a respite from symptoms and signs for three months and went on to recrudescence, with fever and chest pain of the pleuritic type. I postulate that he had an infectious process, which may have been the simple uncomplicated lung abscess type, associated with adjacent pneumonitis. There may have been a foreign body present. The radiologist tells me that some artificial teeth may not be radio-opaque, and therefore may not be seen in a plain film of the chest. There may have been a tuberculoma present, which had not been discovered previously. This may have broken down, emptied and involved the segment in an inflammatory reaction. Many tuberculomas contain live tubercle bacilli, and the presumption is that some would have been seen in the sputum, but their absence is not conclusive evidence against the diagnosis of tuberculosis. Likewise, the absence of cancer cells in the Papanicolaou smear is not definite evidence against cancer of the lung. However, our laboratory has now a very high percentage of positive results by this method. The chronic pneumonitis of the type reviewed by Dr Waddell* recently in this hospital may have a small cavity, 4 out of 10 cases that he has reported had cavities up to 1.5 cm in diameter. I am not able to go any farther with a definite diagnosis than to say that this was a chronic lung abscess, but I still would like to think that there probably was a foreign body in the form of a missing tooth in this area. Tuberculosis may have been found or, likewise, a focus of cancer. I was given the opportunity to study the x-ray films before I presented this case, and was impressed by the ap-

*Waddell: W. R. Sniffen, R. C. and Sweet, R. H. Chronic interstitial pneumonitis: report of 10 cases showing chronic interstitial pneumonitis and unusual deposits of cholesterol. *J. Thoracic Surg.* (in press)

pearance, as Dr Wyman may point out, of an increase in the width of the wall of the cavity noted in the serial films. May we see the films, Dr Wyman?

DR STANLEY M. WYMAN: The lesion described lies in the right mid-chest laterally. There is streaky density extending from the lesion to the hilus. In the lateral view this is seen to lie far posteriorly as recorded, probably in the superior segment of the right lower lobe. The first films do not show conclusively a cavity. The examination, done approximately two months later, shows a more discrete and somewhat larger area of infiltration, with an apparent fluid level, and, as Dr Miller suggests, a thickened wall above. This is seen in the lateral view, and the fluid level is best demonstrated in the lateral projection. One month later the infiltration in the right lower lobe is still larger, and the spot films at this time demonstrate clearly a central area of rarefaction with a probable, small fluid level. The apparent increase in the size of the wall superiorly is seen. Whether this represents actual intrinsic increase in the size of the wall or apparent increase because of atelectasis of adjacent lung, it is impossible to say. Well demonstrated is the pleuritic reaction adjacent to this area of disease. I think it is worth noting that the inner wall of the cavity seems to be smooth, not shaggy or nodular.

DR MILLER: That feature is somewhat against the presence of cancer because in such lesions as we have seen previously there is some irregularity or nodularity of the lining shadow. I might add that the likelihood that this was tuberculoma is very slim. Certainly, in this early picture I would expect a more discrete, clearly rounded, denser shadow if this were a tuberculoma. The possibility of cancer, however, is borne out by several facts. The tendency for density to extend down toward the hilus of the lobe indicates either extension of the process or metastatic obstruction of that segmental bronchus. Also, the fact that, following the return of symptoms three months after the patient was in the hospital the first time, the surgeon elected to proceed with this operation suggests his suspicion of the presence of cancer. Certainly, cancer must be suspected strongly in all these cases, and operation should be done first to make a diagnosis, secondly to cure the patient, if possible, and thirdly, to relieve him of these annoying, terrifying symptoms if possible. I would still, however, persist in my first diagnosis of a nonspecific abscess, with pneumonitis, possibly due to the retention of foreign body, chiefly because of the roentgenographic evidence and the nature of the hemoptysis and of the patient's clinical course.

DR E. B. BENEDICT: I doubt if this was foreign body. If it was a tooth, it probably was the patient's own tooth, and that ought to show by x-ray study or by bronchoscopy. I certainly agree with Dr Miller that the important thing is to treat it as if

it were carcinoma until proved otherwise by explorative thoracotomy.

DR JOHN G. SCANNELL: That is what the patient thought too. He was convinced from the beginning that he had a cancer, and it was difficult not to agree with him. However, when we first saw him, the possibility of an inhaled tooth became apparent and we bronchoscoped him with that in mind. At this time it did appear that the parenchymal shadow was improving, and it was the decision of Dr Churchill and Dr King to follow him closely and meanwhile rule out tuberculosis, which seemed the most likely diagnosis. After three months he began to spit blood again, and with the chance of carcinoma now even more likely, exploration was advised. He was operated on by Dr Churchill, whose pre-operative diagnosis was either carcinoma or tuberculosis.

When the chest was opened the disease process was obviously limited to the superior segment of the right lower lobe. There was no free fluid. The involved segment was firm and injected, but there was no discrete mass and no puckering of the pleura so often seen with carcinoma. On gross inspection the lesion appeared to be benign, in keeping with the diagnosis that Dr Miller has chosen. A segmental resection was done, largely as a biopsy, and inspection of the lesion in the gross indicated that that was all that was necessary. We could find no foreign body, and no apparent cause for the disease.

CLINICAL DIAGNOSIS

Carcinoma?
Tuberculosis?

DR MILLER'S DIAGNOSES

Chronic lung abscess (with foreign body?)
Carcinoma?
Tuberculosis?

ANATOMICAL DIAGNOSIS

Abscess of lung

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: We found a small abscess cavity, 8 mm in diameter, which was surrounded by an area of chronic pneumonitis. There was no foreign body identified. The histologic appearance of the wall of the abscess cavity was characteristic of an organized infectious process of the lung, with many fibrous plugs in the respiratory bronchioles and some in the alveoli. It did not show any marked degree of the lipoid reaction that is seen in many cases with similar histories and similar x-ray findings.

Our diagnosis was a simple abscess of the lung.

DR DANIEL S. ELLIS: Do you ever see such an abscess following an infarct?

DR MALLORY: Almost never, I would say, in the human being. In animal experiments Dr Cutler produced them many times.

CASE 35332

PRESENTATION OF CASE

A thirty-three-year-old woman entered the hospital because of a lump in the right breast

Approximately two years before admission she first noticed an indurated area in the inferior aspect of her right breast. She experienced sharp pain in this area just before the onset of each menstrual period. It changed little in size until she became pregnant sixteen months before entry, when it increased, only to subside again when she miscarried at two and a half months. Ten months before entry she again became pregnant with coincident enlargement of the areas of induration, which again regressed when she miscarried at six weeks. Six months before entry she again became pregnant, and the area markedly increased in size as the pregnancy progressed. She was occasionally bothered by sharp pains in the breast but had no bleeding or discharge from the nipple.

The past history and system review were negative.

Physical examination showed a well developed and well nourished woman in no distress. Inferior to the right nipple occupying most of both lower quadrants of the breast was an ill defined, firm mass within the breast about the size of a tennis ball. There was no retraction of the overlying skin or nipple. The uterus was enlarged to a size consistent with a six-month pregnancy. The remainder of the physical examination was negative.

The temperature was 98.8°F, the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

The routine urine examination was negative.

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. GORDON A. DONALDSON: The one thread running through this history that catches my eye is the fact that this patient of thirty-three had a tumor that was sensitive to the hormones associated with pregnancy. I am going to grasp at that fact to rule out other indurated tumors that might cause the physical features of the tumor described — namely, a low-grade type of abscess, fat necrosis, tuberculosis, sarcoid disease and so forth — and will limit the discussion to chronic mastitis, the fibroadenoma group of tumors and perhaps cancer. I think it is very unlikely that this was cancer or

sarcoma — although there are others here who certainly could elaborate on that point at greater length — because I doubt very much whether a cancer of the breast could be as responsive as this particular tumor was to hormonal factors associated with pregnancy. We do know that some types of cancer change during pregnancy, or increase in size, but I doubt if we should entertain such a diagnosis very strongly in this particular case. So we boil it down to a fibroadenoma with perhaps cystic changes or cystic mastitis itself.

There are several additional points that would be helpful in the history — namely, the condition of the other breast, the presence or absence of axillary changes and a few notes regarding what was seen on simple inspection of the breast. We have been taught that a good deal can be gained by simple inspection of the breast with the patient's hands behind the head, first while sitting up and then lying down. It is also said that 90 per cent of tumors that can be picked up by inspection in such positions prove to be malignant. I think this tumor would probably have been seen on inspection. I doubt very much, however, whether we should consider it malignant. I also doubt if this represented a pericanalicular fibroadenoma, since the tumor was too large. We are therefore left with the possibility of intraductal papilloma, with cystic change. We have a history of no nipple discharge, which would be against such a tumor. The fact that this lesion was indurated and also painful, producing pain with the menses and with pregnancy, is greatly in favor of a mastitic process.

So the presence of a large, indurated tumor, changing under hormonal stimulation and producing pain, leads me to believe that chronic cystic mastitis in some form is probably the best diagnosis.

DR. RICHARD H. WALLACE: I first saw this patient in my office two years before admission, when she said that she had noticed a small lump in her breast two years previously that had not changed in size during the interval. She sought professional advice because she had planned to be married two days later. At that time it measured 3 cm., and was firm. I had the impression that it was a benign tumor, but I advised her to have it removed. We talked over the matter of pregnancy, since the patient stated that she hoped to start a family promptly. I suggested that she have the tumor removed in the near future. I saw her the second

time eighteen months later. She had been married in the meantime, had become pregnant and had miscarried. During the pregnancy the tumor definitely increased in size and subsequently decreased. At the next visit, I should say that the tumor had increased slightly in size, but she again declined surgery because she was leaving the country by air the next day. I saw her again when she was six months' pregnant, at which time she had a tumor measuring 16 cm in greatest diameter. It was more like two tennis balls stuck together, in lobular fashion. The tumor was visible in all positions. The opposite breast was normal for a six months' pregnancy. The axilla had no palpable lymph nodes, and there was considerable dependent edema of the skin in the lower portion of the breast, presumably on a mechanical basis.

DR JOSEPH C AUB: Was it cystic?

DR WALLACE: No cystic areas could be demonstrated.

DR TRACY B MALLORY: Dr Nathanson, would you like to comment?

DR IRA T NATHANSON: These manifestations of the tumor in question are seldom seen because lesions of this type are often removed before pregnancy or are not necessarily responsive to hormonal stimuli. This lesion responded on three occasions during pregnancy in apparently the same fashion as the breast. It also became sensitive and, I judge, enlarged in the pre-menstruum. This probably paralleled an increase in activity of the breast, which appears to be dependent upon hormonal fluctuations during the menstrual cycle. Likewise, during pregnancy and lactation these endocrine stimuli

are increased. I have seen a few other patients who have refused operation on the first occasion. In one case, the patient had a tumor the size of a large grapefruit, which regressed to about 3 cm during involution of the breast following the first pregnancy and lactation. Here, again, the tumor responded to hormonal stimulation during a second pregnancy.

This brings up one point about which there is disagreement — that is, whether fibroadenomas are true tumors or merely represent localized manifestations of breast tissue that are unusually reactive. The latter opinion is one that is held by some of us here.

CLINICAL DIAGNOSIS

Sarcoma of breast?

DR DONALDSON'S DIAGNOSIS

Chronic cystic mastitis

ANATOMICAL DIAGNOSIS

Lactating fibroadenoma of breast

PATHOLOGICAL DISCUSSION

DR MALLORY: The tumor removed was large and kidney shaped, as Dr Wallace has already brought out. The microscopical structure was that of a typical adenofibroma, but the epithelial elements were unusually active, and a large proportion of them, as well as the surrounding normal breast tissue, showed evidence of secretion as one would expect at six months' pregnancy.

CASE 35332

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Many other therapeutic points could be mentioned. There remains, however, no substitute in a therapeutic dilemma of this magnitude for sound clinical knowledge and observation, and a thorough grounding in the physiologic principles underlying rational cardiovascular therapy.

POLIOMYELITIS—A DIAGNOSTIC PROBLEM

WITH the arrival of the poliomyelitis season, the problem of diagnosis again comes to the fore. Little difficulty is, of course, encountered with the cases exhibiting frank paralysis. In recent years, however, physicians have been attempting to recognize the nonparalytic form of the disease. Here the diagnostic problem becomes exceedingly difficult.

The differences of opinion that arise among groups of physicians were illustrated in an incident in Massachusetts in 1948. In the central portion of the State two communities side by side were having illnesses probably due to the same virus. In one, the pattern was to call the illness lymphocytic choriomeningitis—in the other, meningitis of undetermined origin. A short distance away a large group of cases occurred in another community where it may well have been that the same virus was operating. In this community the cases were called poliomyelitis.

In the absence of a laboratory diagnostic test, it is impossible to say which of the three groups of physicians correctly diagnosed the condition. The absence of paralysis in all the cases makes the diagnosis of poliomyelitis quite unlikely. This incident emphasizes the ease with which an incorrect diagnosis can be made in such borderline cases.

Poliomyelitis started early in Massachusetts in 1949. Whether this foretells an epidemic year or whether it merely indicates an early poliomyelitis

season cannot be determined until the trend of the disease in the immediate future can be ascertained. The comparatively higher prevalence since 1944 may indicate that the disease is spread over a period of four or five years instead of having a short one-year outbreak. The return to the normal proportion of two-thirds paralytic to one-third non-paralytic cases may indicate that the confusing virus prevalent in 1948 may be of less importance this year. Last year two-thirds of the diagnosed cases were nonparalytic.

ROSEOLA

ONE of the commonest diagnostic errors that occur in pediatric practice is the failure to differentiate roseola infantum (or exanthem subitum) from other febrile affections—especially pharyngitis, measles and German measles. The excellent paper by Berenberg, Wright and Janeway that appears elsewhere in this issue of the *Journal* provides a critical analysis of this somewhat enigmatic disease and should be of service in reminding the practitioner of the possibility of its occurrence.

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Roseola, on account of its ordinarily mild nature, is not commonly seen in hospital practice—181 cases were observed at the Children's and Infants' hospitals in the ten-year period from 1937 to 1947. This group, however, representing more than mildly sick patients, indicates the latent possibilities for mischief that exist with almost any viral infection.

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CARDIAC CONTRAINDICATIONS TO SURGICAL PROCEDURES

THE patient with heart disease who develops a disorder requiring surgical intervention often presents a taxing therapeutic dilemma to the attending physician. To withhold surgery may be almost certainly fatal, but to permit a major surgical procedure in the face of serious heart disease may seem equally foolhardy. The surgeon and the anesthetist have done a great deal to minimize the danger of operation to patients with heart disease. Improvements in surgical technics, anesthetic agents and insistence on the constant maintenance of an adequate supply of oxygen represent major advances in the direction of safe operation for cardiac patients. But the dilemma still recurs, although less frequently than was formerly the case.

From the point of view of the cardiologist, heart disease itself is not necessarily a contraindication

Nevertheless, many patients who need elective and occasionally some who need emergency operations are denied proper surgical treatment merely because of the presence of valvular, hypertensive or some other type of heart disease. On this basis alone, such a stand may not be justified.

When the time factor is not of prime importance, the cardiac contraindications to elective procedures may be defined with fair precision. In this situation, there are at least five such contraindications: cardiac decompensation, acute myocardial infarction, acute, paroxysmal arrhythmias, active myocarditis or pericarditis and bacterial endocarditis. In cases of cardiac decompensation, whatever the etiology of the heart disease, compensation should be restored before elective operation is attempted. Likewise, an acute myocardial infarct must be allowed to heal before the procedure is carried out. Paroxysmal arrhythmias must be abolished or controlled. Active involvement of the myocardium or pericardium, whether rheumatic or due to some other etiologic agent, should be allowed to subside before operation is undertaken. Bacterial endocarditis is such a serious disease in itself that no elective surgical procedure should be considered until it is controlled by appropriate treatment with antibiotics. Very severe coronary vascular disease with angina pectoris may constitute another contraindication. Milder grades of the disease seldom do so, although the patient should be protected with extreme care from oxygen lack and blood loss during operation.

In surgical emergencies, such as acute intestinal obstruction and common-duct stone, one may be driven to ignore the cardiac contraindications. Chances may have to be taken to serve the patient's best interests. Even in such desperate situations it is usually possible to minimize the risk to the patient if the surgeon, cardiologist and anesthetist pool their knowledge and deal with the problem along physiologic lines. In addition to proper use of cardiac drugs, the patient's tolerance for intravenous fluids must not be exceeded. Intravenous administration of saline solution is often a deadly agent in cardiac patients and seldom has a logical place in their preoperative or postoperative management. The principle of fluid replacement therapy

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MASSACHUSETTS MEDICAL SOCIETY



COMMITTEE ON LEGISLATION

One of the most controversial issues before the Massachusetts General Court during the current legislative session was the Cash Sickness Compensation Bill. This bill was strongly supported and strongly opposed. Hearings were stormed and noisy.

The bill provided for a state-operated monopolistic compulsory cash sickness program for workers. Major argument hinged chiefly upon this proviso. A spokesman for the CIO stated before committee, "I think this is legislation that is long overdue. It happens to be in the Governor's message and I want to say very emphatically that if we don't get a state fund program, we are on record that we will accept no cash sickness at all. We will ask the legislature to defeat it if the committee doesn't report it favorably, and we will ask the Governor to veto it because the workers want no part of profiteering in human misery and sickness."

The Cash Sickness Compensation Bill was finally defeated by the narrow margin of three votes. The problem is now slated for study by a commission. The brief filed by direction of the Committee on Legislation of the Massachusetts Medical Society follows:

STATEMENT OF THE MASSACHUSETTS MEDICAL SOCIETY ON HOUSE NO. 2591, THE CASH SICKNESS COMPENSATION BILL, FOR THE COMMITTEE ON WAYS AND MEANS OF THE MASSACHUSETTS GENERAL COURT

The Massachusetts Medical Society finds itself not in complete agreement with House No. 2591, the Cash Sickness Compensation Bill, as it now stands.

This bill has been carefully studied by the Society since printed copies became available. It is not our purpose to single out points we would praise or condemn as private citizens and voters interested in the broad problems of the public health.

Our principal function as a medical society is to view this, as all other legislation pertaining to health, as working for or against the best possible standards of medical progress and the mental and physical health of the public.

Under this bill as drawn the physician is held responsible for the medical operation of the sickness compensation plan. The claimant for benefits must have filed a physician's certificate (Sec. 7 [a] [4]) and, "if directed to do so by the director, [shall] have submitted to a medical examination for the purpose of determining his sickness" (*Idem*).

In practice this requirement would charge practicing physicians not only with administrative responsibilities but with underwriting responsibility as well. E. H. O'Connor, managing director, Insurance Economics System of America, has stated, "As these state plans begin to expand, as is evident from legislative bills introduced in Rhode Island, California and New Jersey, more benefits will be paid and the cash sickness benefits of a state fund must be protected. It will naturally follow that

the state will be forced to set up rules and regulations for the certification of claimants."

Solvency of a state fund might be protected if it were possible to determine ability to work in all instances through promulgation of rules and regulations and the application of existing medical knowledge. Every physician knows there are many instances where it is absolutely impossible to determine medically whether a person is or is not able to work.

This is particularly true in cases of mental illness. The definition of "sickness" (Sec. 3 [m]) contains the words

"because of his physical or mental condition, he is unable to perform his regular or customary work." It was stated in Federal Security Administrator Oscar R. Ewing's report to the President that from 30 to 50 per cent of all persons consulting doctors have complaints due at least in part to emotional disorders. For the evaluation of these complaints it is stated 4500 psychiatrists are available in this country where some 15,000 are needed.

From the point of view of the medical profession, charged with the responsibility of certification and professional administration, it cannot be too much emphasized that this program concerns itself essentially with temporary disability. Experience has shown the importance of adequate administrative control for the successful operation of such plans. We wish to stress that the evaluation of conditions of temporary disability depends upon factors which are at best 50 per cent subjective.

The dangers to the solvency of the cash sickness compensation fund from malingering have been recognized by the architects of this bill. "He [the director] shall also publicize the potential results of malingering" (Section 18). In view of what has been said above concerning the subjective factors of temporary disability it must be made clearly apparent that merely designating the physician as the policeman is not the answer. There are no magic tests for the evaluation of purely subjective symptoms.

For the 6750 physician fellows of the Massachusetts Medical Society we feel we can promise full co-operation within the code of ethics of the Society and of the American Medical Association within the limitations previously noted. We point out, however, that no criteria for diagnoses are established within the bill and there is no provision for a medical advisory board to assist in this and other important functions under the bill.

The bill defines a "physician" (Sec. 3 [r]) as "an individual licensed to practice medicine or dentistry under the laws of this or any other state." For some 2500 physicians licensed to practice in Massachusetts the added ethical controls over fellows of the Massachusetts Medical Society are absent. For them the basic legal controls of malpractice laws are the limits to which they can be held.

Under Section 8 *Claims and Appeals* (c) provision is made for calling as an expert witness any medical adviser appointed by the director. There is no provision made for establishing the qualifications of such experts.

In view of the tremendous responsibilities placed upon the individual physician and upon the medical profession in the administration of this plan, we seriously question the absence of the physician's voice in the setup for administrative control.

This defect is the more notable since Section 12 *Penalties* states, "Any person convicted of a violation of any provision of this chapter or of a violation of any order, rule or regulation of the director or of the division made under the authority of any provision of this chapter, the punishment for which is not otherwise provided, shall be punished by a fine of not more than fifty dollars for the first offense, and for any subsequent offense within a period of two years immediately following his final conviction of a like offense by a court of the Commonwealth, shall be punished by a fine of not less than fifty dollars nor more than two hundred dollars, or by imprisonment for not more than two years, or both."

Respectfully submitted for the President and fellows of the Massachusetts Medical Society

JOHN F. CONLIN, M.D.
Director of Medical Information and Education

cases occur between the ages of six months and three years. Its most characteristic feature is that the rose-pink, somewhat morbilliform rash occurs almost invariably at the time of defervescence from a three-day to five-day fever, and actually, unlike the eruptions of most of the acute exanthemata, marks the beginning of convalescence. Attention to this one striking characteristic would prevent many a mistaken diagnosis.

No specific viral agent has yet been isolated, and the relatively rare spread by contact, with occasional apparent instances of unusually long incubation periods, marks roseola as a disease of "poorly defined communicability." Despite its almost invariably good prognosis, roseola may nevertheless occur as a severe infection with convulsions as its commonest complication. This is suggestive of the group of viral diseases that require continued study in view of the insidiousness of the attack and the remoteness of the consequences.

WASHINGTON REPORT ON THE MEDICAL SCIENCES

THE idea of the temple on the hill dates back, no doubt, to the earliest sacrificial altar. The geographic elevation placed the worshiper a little nearer to the object of his veneration, in addition to which his devotions could more easily be observed by the less exalted members of the tribe. The Tower of Babel provides an extreme example of carrying a good thing too far.

The custom, once sacred, has become secular as well. The modern state places its seat of government also on a hill, probably to make it appear a little nearer to the source of divine guidance, perhaps also to catch the cooling breezes that have been so conspicuous by their absence from Capitol Hill this summer.

Capitol Hill seems to generate heat, in fact, rather than escape it. The case of socialized medicine, which had been under control for a number of weeks, burst into flame again in late July with the introduction of President Truman's reorganization plan, including the creation of a Department of Welfare. With the country heading toward the footing of

a welfare state, this would presumably become the tail that wags the dog. In its defense Mr. Ewing, according to *Washington Report on the Medical Sciences*, of July 25, "disavowed charges that have been made that elevation of FSA to Department rank would bring new prestige and new powers that would be employed for all they were worth toward achievement of national compulsory health insurance." The plan, he stated, contains nothing that would add to the authority he already possesses, to which he subjoined rather naïvely, "Besides, the President has not told me he intends to appoint me as the new Secretary."

A Department of Health with a physician as Secretary is desired in many quarters instead of a Department of Welfare and is being supported by the American Medical Association. The question whether the Secretary should be of necessity a physician can be argued. Secretaries of War and of the Navy have usually been laymen, and better so, the Secretary of Labor is not commonly a laborer, although the country has always breathed more freely when the Secretary of State was a statesman.

Sometimes half a loaf, buttered, is better than a whole loaf, dry.

Veterans Administrator Carl R. Gray, Jr., has finally conceded that Dr. Paul B. Magnuson, chief medical director, should be in direct charge of the Administration's medical program. He has acknowledged in writing, also according to *Washington Report on the Medical Sciences*, that the sole purpose of operating veterans hospitals is the care and treatment of patients.

An opinion is prevalent, that a physician, who is a writer, must be a poor practitioner, therefore, an author, however distinguished, cannot compete with a neighbor who may not be able to write his mother tongue grammatically. In other words, a man cannot be successful in both, and hence the public sentiment, to an extraordinary extent, is decidedly in favor of a physician who does not trouble himself with books, or divert his mind from the grave consideration of visiting patients, by interesting himself in the details of science.

Boston M. & S. J., August 15, 1849

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AUREOMYCIN IN THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN*

BENNETT OLSHAKER, M.D.,† SIDNEY ROSS, M.D.,‡ ADRIAN RECINOS, JR., M.D.,§ AND
ELLSWORTH TWIBLE, M.D.†

WASHINGTON, D. C.

AUREOMYCIN is an antibiotic derived from a strain of *Streptomyces aureofaciens*. The drug has been found to have a wide antibacterial spectrum against gram-positive and gram-negative organisms. In addition, it has been found to be effective against rickettsia as well as certain viruses chiefly of the lymphogranuloma-venereum-psittacosis group.¹ In man therapeutic doses up to 60 mg per kilogram of body weight per day given orally have not been associated with toxic manifestations except for occasional nausea, vomiting and diarrhea. These symptoms have been transient and do not contraindicate or prevent continuation of therapy.

Aureomycin is absorbed readily after oral administration, and the maximum rate of excretion in the urine occurs between four and eight hours after the dose.² Thus, an interval between doses of four to six hours can be considered optimum. The oral route is the preferable mode of administration. Intramuscular injection is accompanied by local pain and sometimes induration and tenderness. Aureomycin may be given intravenously, but this method of administration was not employed in our series.

A study to evaluate the efficacy of aureomycin[®] in the treatment of pneumonia in infants and children was instituted in January, 1949. This investigation was prompted by the observation that the drug is effective against the bacteria most frequently responsible for pneumonia and by published reports of its value in the treatment of atypical viral pneumonia.^{3, 4} It has been found that strains of pneumococcus, streptococcus and *Hae-*

mophilus influenzae are almost completely inhibited by aureomycin in concentrations of 1 microgm per cubic centimeter or less.⁵ Such a blood concentration is readily obtained with therapeutic doses of the drug. Recently, Schoenbach and Brer² and Finland and his co-workers⁴ reported small series of cases of primary atypical pneumonia that responded well to aureomycin. This constitutes the first indication of any effective antibiotic agent in viral pneumonia, all previous therapy having been found to be ineffective.

Thus, aureomycin, because of its versatility, seems to be an extremely valuable agent in the treatment of pneumonia. A drug that is effective against both viruses and bacteria embraces a considerably larger antimicrobial range than either sulfadiazine or penicillin (or both combined) and should be effective against the vast majority of pneumonias encountered in the pediatric age group.

MATERIALS AND METHODS

In view of these considerations it was believed that aureomycin warranted a clinical trial. To this end, a special pneumonia ward was set up at the Children's Hospital. So far as possible consecutive patients who had clinical and roentgenologic evidence of pneumonia were treated with aureomycin on admission to the hospital. These patients either had not received previous therapy or had not been benefited by chemotherapy or antibiotics.

A uniform plan of study was employed in all cases, including nasopharyngeal and blood cultures, blood counts, x-ray examination of the chest, agglutinins for streptococcus MG and cold hemagglutinins at periodic intervals during the course of therapy. Nearly all the patients were seen in the follow-up clinic approximately three weeks after the onset of illness. At this time each patient was re-examined, and blood was drawn for follow-up streptococcus MG and cold hemagglutinin titers.

Examination of the flora of the nasopharynx has been reported to be a fairly reliable procedure in determining the causative agent of pneumonia in children.⁶ It should be remembered, however,

*From the Research Foundation of the Children's Hospital.

This study was supported by a grant from the Antibiotic Study Section of the Division of Research Grants and Fellowships, The National Institutes of Health, United States Public Health Service and was conducted under the auspices of the Antibiotic Committee of the Children's Hospital composed of Drs. E. Clarence Rice, Frederic G. Burke and John A. Washington.

†Resident, Children's Hospital.

‡Instructor in pediatrics, George Washington University School of Medicine, junior attending physician, Children's Hospital, research fellow, National Institute of Health.

§Instructor in pediatrics, Georgetown University School of Medicine, chief resident, Children's Hospital.

[®]Kindly supplied by the Lederle Laboratories Division, American Cyanamid Company, New York City.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SCARLET-FEVER STREPTOCOCCUS ANTITOXIN

The Division of Biologic Laboratories of the Massachusetts Department of Public Health discontinued the production and distribution of scarlet-fever streptococcus antitoxin on August 10, when the small stock reached its expiration date. Owing to the small amount of the antitoxin used in recent years, it would be an economic loss for the Department to continue its manufacture.

REFRIGERATION STORAGE OF VACCINE

The following letter regarding refrigeration storage of vaccine is believed to be of interest to physicians:

Geoffrey Edsall, M D
Antitoxin and Vaccine Laboratory
Massachusetts Department of Public Health
Forest Hills, Massachusetts

Dear Dr Edsall:

I thought you might be interested to know that at the Brookline Friendly Society, where we vaccinate somewhat more than 125 children a year, we have, using the Massachusetts vaccine, which is obtained from the Laboratory on the same morning on which the vaccinations are administered, had a 100 per cent take on the first vaccination for four successive years—in a group totaling well over 500 children—without a miss. The ages range from six months to three years, most of them being in the age group from six months to one year. Your product and the methods of storage that you employ are certainly as nearly perfect as anything could be.

Incidentally, it is interesting to note that my batting average is very much lower here in the office, owing, I am sure, to the fact that we are not able to keep the vaccine constantly below freezing.

Very sincerely yours,

RICHARD C TEFFT, JR., M D

266 Beacon Street
Boston

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The September schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	September 7	William T. Green
Brockton	September 8	George W. Van Gorder
Lowell	September 9	Albert H. Brewster
Salem	September 12	Paul W. Hugenberger
Greenfield	September 12	Charles L. Sturdevant
Gardner	September 13	Carter R. Rowe
Worcester	September 16	John W. O'Meara
Springfield	September 20	Garry deN. Hough, Jr.
Pittsfield	September 21	Frank A. Slowick
Hyanis	September 22	Paul L. Norton
Fall River	September 26	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

UNITED COMMUNITY SERVICES

Dr. Philip D. Bonnet, Massachusetts Memorial Hospitals, will head the Hospital Group of the Service Division in the Red Feather campaign of 1949. Dr. Bonnet has been affiliated with the Red Cross and other social agencies in Philadelphia, where, until 1948, he was hospital administrator of Lankenau Hospital.

CORRESPONDENCE

UNWARRANTED PUBLICITY

To the Editor: Unfortunately considerable publicity, even in professional circles, has been given to a recent newspaper release concerning tonsillectomies performed on five youngsters in one family at the Malden Hospital on the same morning by Dr. Joseph Gitter of Malden.

It is indeed unfortunate that a newspaper "human interest" story should be so exploited. The children were service patients, all on Aid to Dependent Children, the occasion, a T and A clinic. Dr. Gitter, acting in the charitable capacity of senior surgeon on service, was unaware that some of the patients on whom he was operating in the course of the morning were related.

Officially, the hospital only gave permission for a photograph at the door upon discharge, the balance of the information, including the surgeon's name, was secured by the usual enthusiastic newspaper men from the usual "un-named sources."

WILLIAM S. BRINES, Director

The Malden Hospital
Malden, Massachusetts

NOTICES

ANNOUNCEMENTS

Dr. Samuel Bachrach announces the removal of his office to the Medical Arts Building, 36 Pleasant Street, Worcester, Massachusetts.

Dr. William M. Downing announces the removal of his office from 1180 Beacon Street, Brookline, where he was associated with Dr. Clifford C. Franseen. He has associated himself with Drs. H. Irving Bixby and Milton E. Johnson, First National Bank Building, Attleboro, for the practice of general surgery.

Dr. William J. Halpin announces the removal of his office from 5 Luther Road, Medford, to 307 Winthrop Street, Medford.

Dr. Douglas A. Thom announces the removal of his office to 459 Marlboro Street, Boston.

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH POSTGRADUATE SEMINAR IN NEUROLOGY AND PSYCHIATRY

The Fifteenth Seminar in Neurology and Psychiatry will begin October 3, 1949, and will continue until May 19, 1950. It will consist of three separate courses running concurrently as follows:

Review Course in Basic Neurology and Psychiatry, 66 lectures, every Friday, 2:00 p.m. to 8:30 p.m. from October 7 to December 9, 1949, and from March 3, to May 19, 1950, at the Metropolitan State Hospital, 475 Trapelo Road, Waltham, Massachusetts.

Course in Social and Special Psychiatry, 36 lectures every Wednesday, 5:30 to 10:00 p.m. from October 19 to December 14, 1949, and from March 15 to May 10, 1950, at the Boston Psychopathic Hospital, 74 Fenwood Road, Boston, Massachusetts.

Course in Pediatric Neuropsychiatry (Child Psychiatry), 20 lectures, every Monday, 6:00 to 9:30 p.m. from October 3 to December 5, 1949, at the Walter E. Fernald State School, Waverley, Massachusetts.

All interested graduate physicians should apply before October 1, 1949, by writing to Dr. William C. Gaebler, Superintendent, Metropolitan State Hospital, Waltham, Massachusetts.

The applicants should indicate which of the three courses of the seminar they wish to attend. The registration is requested as a matter of courtesy to the institutions where courses are conducted, also as a convenience for the registrants who will thus receive the schedules and be notified if changes should become necessary during the year.

(Notices concluded on page xxxi)

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A uniform plan of study was employed in all cases, including nasopharyngeal and blood cultures, blood counts, x-ray examination of the chest, agglutinins for streptococcus MG and cold hemagglutinins at periodic intervals during the course of therapy. Nearly all the patients were seen in the follow-up clinic approximately three weeks after the onset of illness. At this time each patient was re-examined, and blood was drawn for follow-up streptococcus MG and cold hemagglutinin titers.

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¶Kindly supplied by the Lederle Laboratories Division, American Cyanamid Company, New York City.

that isolation of an organism from the nasopharynx is, at best, only partial evidence that it is the organism responsible for the disease in the lower respiratory tract. In the opinion of Alexander et al.⁷ the presence of substantial numbers of pneumococci in the nasopharynx of a child with pneumonia is a reliable index that the patient has pneumococcal pneumonia. The presence of a beta-hemolytic streptococcus or *H. influenzae* as the sole or predominant organism is only probable evidence that it is the pathogen in the lower respiratory tract. However, the isolation of hemolytic *Staphylococcus aureus* has little or no significance in determining the etiologic agent in pneumonia since it is found so frequently in the nasopharynx of normal children. A positive blood culture, of course, is presumptive evidence of the responsible organism of an associated pneumonia.

Thirty-nine patients fulfilling the established diagnostic requirements of pneumonia were studied. Their ages ranged from three months to eleven years and were distributed as follows: 3 patients were less than six months of age, 3 between six and twelve months, 10 from one to two years, 12 between two and five years, and 11 from six to twelve years.

Of the 39 cases in this series, 30 were classified as bacterial and 9 as viral in origin (Table 1). A pneumococcus was isolated in 16 of the 30 cases of bacterial pneumonia and a beta-hemolytic streptococcus in 2. *Staph. aureus* was cultured from the blood of an infant with a severe bilateral bronchopneumonia. The organisms cultured from the naso-

TABLE 1 Classification of 39 Cases of Pneumonia

TYPE OF PNEUMONIA	No. of CASES
Bacterial	30
Pneumococcal	16
Streptococcal	2
Staphylococcal	1
Unclassified	11
Primary atypical	9

pharynx of the 11 unclassified patients represented the normal nasopharyngeal flora, including *Staph. aureus*, *Staph. albus*, *Streptococcus viridans* and *Neisseria catarrhalis*. The mere presence of these organisms in the upper respiratory passage was not considered sufficient to indict them as the causative agents of the pneumonia. However, the clinical manifestations together with the x-ray findings and leukocytosis were compatible with a diagnosis of bacterial pneumonia in this unclassified group.

In evaluating the efficacy of a new drug the severity of the illness should be taken into consideration. It was considered marked in 15 of 39 cases (38.4 per cent), moderate in 11 (28.2 per cent) and mild in 13 (33.4 per cent). Eight of the patients required oxygen. The children with bacterial pneu-

monia were in general more severely ill on admission than those with the viral cases.

The temperature of the patients in this series at the time of initiation of therapy ranged from 100.2 to 106°F. In 25 cases it was above 103°F. Patients in the bacterial group generally ran higher temperatures, 22 (73 per cent) having temperatures above 103°F at the time of admission.

White-cell counts are usually elevated in pneumonias of bacterial origin and normal or depressed in the viral types. In our cases all but 1 patient with bacterial pneumonias had white-cell counts above 10,000 on admission, and 6 of the 9 with viral pneumonias had counts below 10,000.

RESULTS

The therapeutic effect of aureomycin on the pneumonias of bacterial origin was quite favorable. The

TABLE 2 Results in 39 Cases of Pneumonia Treated with Aureomycin

TYPE OF PNEUMONIA	GOOD	RESULT FAIR	POOR
Bacterial			
Pneumococcal	14	2	—
Streptococcal	1	1	—
Staphylococcal	1	—	—
Unclassified	8	2	1
Primary atypical	7	1	1
Totals	31	6	1

over-all results (based principally on the rapidity of return to normal of clinical, roentgenologic and laboratory findings) were considered good in 24 cases, fair in 5, and poor in only 1. The results were particularly gratifying in the pneumococcal group, 14 of 16 patients showing a good response (Table 2). It is interesting that the unclassified bacterial pneumonias demonstrated a less dramatic response than the cases on which a specific organism was indicted.

In 15 (50 per cent of the 30 cases of bacterial pneumonia) the temperature returned to normal eighteen hours after initiation of aureomycin therapy. Four patients became afebrile in eighteen to thirty-six hours, and 9 maintained an elevated temperature from thirty-six to seventy-two hours. Two other patients had low-grade fevers beyond seventy-two hours, 1 for ninety-six and the other for one hundred and twenty hours. It is interesting that 9 of the 11 patients who maintained a temperature elevation beyond thirty-six hours had received aureomycin intramuscularly. In 2, a change from the intramuscular to the oral mode of administration produced a prompt defervescence within twelve to twenty-four hours.

Two infants with pneumococcal pneumonia had an associated pertussis and ran a protracted low-grade fever in spite of apparent early improvement of the pneumonia.

An evaluation of the effect of aureomycin on the pathogens of the nasopharynx was attempted. Cultures were obtained on the first, third and fifth hospital days on each patient. Of the 16 cases of pneumonia in which a pneumococcus was the predominant organism initially, 7 failed to grow out this pathogen on the second or subsequent cultures. In 4 others pneumococci were not demonstrable on the third culture. However, in 5 cases the organism was still present in the nasopharynx after five days of aureomycin therapy. There was no apparent correlation between the interval required for the elimination of the pathogen from the nasopharyngeal cultures and the over-all clinical improvement.

Serial white-cell counts were analyzed in the patients with bacterial pneumonia treated with aureomycin. In 71 per cent of the cases of pneumococcal pneumonia the white-cell count returned to normal (5000 to 10,000) within five days of the initiation of therapy. Six of 10 patients (60 per cent) with unclassified bacterial pneumonia showed an equally prompt drop to normal after aureomycin was started. In general the decline in the white-cell count was more rapid in children who were given the drug by mouth than in those who received it intramuscularly.

Each of the patients had an x-ray examination of the chest on the day of admission. Follow-up films were taken on all but 1 child and the majority were examined roentgenologically three or more times. A strict evaluation of the effect of aureomycin on the lesion radiologically was not possible because of the slight discrepancy in the intervals between films among the patients in the series. However for purposes of classification, the patients were arbitrarily divided into those who showed appreciable resolution by x-ray study in seven days or less and those in whom there was little or no change in that time. There was evidence of considerable resolution of the inflammatory process within seven days in 23 of 30 patients with bacterial pneumonia. A rather striking difference was noted in the roentgenologic results in the patients with bacterial pneumonia treated orally and in those treated intramuscularly. Sixteen of the 17 cases of pneumonias treated orally resolved appreciably within seven days whereas only 7 of 13 cases treated intramuscularly had shown resolution by x-ray examination in that time.

TREATMENT OF BACTERIAL PNEUMONIAS

The pertinent data of the 30 cases in the bacterial group are summarized in Table 3. The following 4 cases serve to illustrate the course of the various types of bacterial pneumonia treated with aureomycin.

S. L., a 7-year-old Negro, contracted a respiratory infection about 1 week before admission. For 2 days before entry he complained of pain in the left side of the chest that was ag-

gravated by breathing. Associated symptoms included cough, headache, malaise and fever.

Physical examination revealed an acutely ill child with rapid, grunting respirations. The temperature was 103°F. The pharynx and tonsils were reddened, and there were dullness and diminished breath sounds over the left lower portion of the chest posteriorly. The white-cell count was 27,700, with 84 per cent neutrophils. Pneumococci and beta-hemolytic streptococci were cultured from the nasopharynx and a blood culture was sterile. X-ray examination of the chest revealed an area of density in the medial two thirds of the lower left portion of the chest. The clinical course and other pertinent data are shown in Figure 1.

Shortly after admission aureomycin therapy was initiated in a dose of 250 mg orally every 4 hours. The temperature dropped rapidly to normal eighteen hours after therapy was started, and concomitantly the patient showed a striking clinical response. Subsequent nasopharyngeal cultures failed

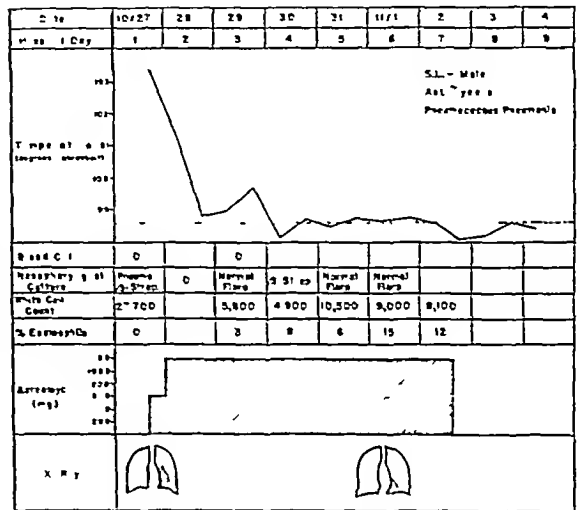


FIGURE 1. Clinical Course and Laboratory and X-Ray Findings in S. L.

to grow out any pneumococci. Therapy was discontinued on the sixth day after an uneventful recovery.

T. D., a 5-year-old boy, was admitted to the hospital with a respiratory infection accompanied by cough of 3 days' duration. On the day before entry he became worse, with rapid respirations, a more severe nonproductive cough, pain in the left side of the chest, listlessness and anorexia.

Physical examination revealed a moderately ill, dyspneic child with a temperature of 102°F. There was dullness to percussion, and the breath sounds were diminished over the left side of the chest posteriorly.

The white-cell count was 18,500 with 75 per cent neutrophils. A blood culture was sterile. Beta-hemolytic streptococci were cultured from the nasopharynx. X-ray study of the chest revealed an area of opacity involving most of the left lower lobe and considerable infiltration throughout the right side of the chest. The course and other pertinent data are shown in Figure 2.

Aureomycin therapy was instituted shortly after admission in a dosage of 250 mg orally every 4 hours. Within 16 hours of admission the patient was afebrile and appeared much improved. The abnormal chest signs cleared gradually, and on the 6th hospital day there was x-ray evidence of complete resolution. The drug was discontinued after 5 days, and on the 6th hospital day the child was discharged after an uneventful convalescence.

V. F., a 10-week-old Negro infant, was well until 3 days before admission, when she began to cough and had a high fever and difficulty in breathing. These symptoms increased in severity until the time of hospitalization.

Physical examination disclosed an acutely ill, dyspneic infant with a temperature of 104.8°F, a pulse of 200 and respirations of 120 per minute. There were coarse and crepitant rales at both bases. The white-cell count was 26,000, with 49 per cent neutrophils and a predominance of immature

The patient was placed in an oxygen tent, and aureomycin was administered intramuscularly in a dosage of 10 mg every 8 hours. The infant improved rapidly, and in 12 hours was afebrile and out of oxygen. Except for slight rises in temperature on the 2nd and 4th hospital days, recovery was un-

TABLE 3 Summary of 30 Cases of Bacterial Pneumonia Treated with Aureomycin

CASE No	PATIENT	AGE	TEMPERATURE	SEVERITY	LOCATION	NASOPHARYNGEAL CULTURE
1	S. L.	yr 7	103.0	Moderate	Left lower lobe	Pneumococcus beta hemolytic streptococcus
2	S. M.	1 10/12	104.0	Marked	Right (bronchopneumonia)	Pneumococcus <i>N. catarrhalis</i>
3	H. C.	7	103.4	Marked	Right upper lobe	Pneumococcus gamma streptococcus staphylococcus (nonhemolytic)
4	N. H.	7	104.4	Moderate	Left lower lobe	Pneumococcus <i>N. catarrhalis</i>
5	W. S.	7	104.4	Mild	Left upper lobe	Pneumococcus <i>N. catarrhalis</i> <i>H. influenzae</i>
6	G. M.	8/12	104.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (hemolytic) <i>H. influenzae</i>
7	D. G.	4	105.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (hemolytic)
8	J. T.	3	104.0	Moderate	Right lower lobe	Pneumococcus <i>Staph. aureus</i> (hemolytic)
9	B. T.	1 4/12	106.0	Mild	Right lower lobe	Pneumococcus <i>N. catarrhalis</i>
10	A. C.	1 10/12	104.8	Moderate	Right upper lobe	Pneumococcus <i>N. catarrhalis</i> <i>Staph. aureus</i> (non hemolytic)
11	M. P.	9/12	105.0	Marked	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (hemolytic)
12	R. C.	2 4/12	103.0	Marked	Right and left (bronchopneumonia)	Pneumococcus
13	P. F.	1 4/12	105.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (hemolytic)
14	W. S.	6	104.0	Mild	Left lower lobe	Pneumococcus
15	V. B.	8/12	101.0	Marked	Right and left (bronchopneumonia)	Pneumococcus <i>Haemophilus pertussis</i> <i>Escherichia coli</i> <i>Staph. aureus</i> (nonhemolytic)
16	E. J.	3/12	102.6	Marked	Right (bronchopneumonia)	Pneumococcus <i>H. pertussis</i> <i>Staph. aureus</i> (hemolytic)
17	A. C.	6	103.0	Marked	Right lower lobe	Beta hemolytic streptococcus <i>N. catarrhalis</i>
18	T. D.	5	102.0	Mild	Left lower lobe	Beta-hemolytic streptococcus
19	V. F.	3/12	104.8	Marked	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (nonhemolytic)
20	V. L.	9/12	101.0	Marked	Right and left (bronchopneumonia)	<i>Esch. coli</i> (hemolytic) gamma streptococcus
21	J. B.	10	105.2	Marked	Right and left (bronchopneumonia)	<i>Staph. albus</i> (hemolytic) gamma streptococcus
22	G. W.	2	103.4	Moderate	Right and left (bronchopneumonia)	<i>N. catarrhalis</i> <i>Staph. aureus</i> (nonhemolytic)
23	D. G.	1 7/12	104.8	Moderate	Right and left (bronchopneumonia)	<i>Staph. aureus</i> (hemolytic) <i>N. catarrhalis</i>
24	B. L.	2	102.4	Mild	Right lower lobe	<i>Staph. aureus</i> (hemolytic) pneumococci (few)
25	H. B.	5	104.6	Mild	Right and left (bronchopneumonia)	<i>Staph. aureus</i> (hemolytic)
26	R. L.	6	103.6	Marked	Right and left (bronchopneumonia)	<i>Staph. albus</i> (hemolytic)
27	W. D.	5/12	103.0	Marked	Right and left (bronchopneumonia)	<i>N. catarrhalis</i> <i>H. influenzae</i> <i>Staph. albus</i> (hemolytic)
28	W. T.	2	104.4	Mild	Right and left (bronchopneumonia)	<i>Staph. aureus</i> (nonhemolytic)
29	H. M.	1 5/12	100.2	Marked	Right and left (bronchopneumonia)	<i>N. catarrhalis</i> <i>Staph. albus</i> (nonhemolytic)
30	D. S.	6	100.4	Mild	Right (bronchopneumonia)	Gamma streptococcus

*Intramuscular injection

†Oral administration

forms. Hemolytic *Staph. aureus* was cultured from the blood, and nonhemolytic *Staph. aureus* and pneumococcus were isolated from the nasopharynx. X-ray study of the chest revealed a disseminated bronchopneumonia. The course and other data are shown in Figure 3.

eventful. Subsequent blood cultures were negative, and aureomycin was discontinued after 8 days.

The patient in the bacterial group who was considered not to have benefited by aureo-

mycin was a six-year-old boy who was admitted to the hospital with a severe bronchopneumonia associated with measles that had previously not responded to penicillin and failed to im-

normal within three and a half days. An associated hematuria, albuminuria and pyuria were noted on several urine specimens during the hospital stay. Thus, the evaluation of

TABLE 3 (Continued)

CASE NO	MAXIMUM WHITE CELL COUNT	PREVIOUS THERAPY	AUREOMYCIN THERAPY			RESULTS
			DAY INITIATED	DOSAGE mg/kg/24 hr	TOTAL DURATION days	
1	27 000	None	4	41.0	6	Patient afebrile in 18 hr. x-ray evidence that chest had cleared in 6 days. recovery uneventful.
2	40 300	None	5	46.0	6	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 4 days. recovery uneventful.
3	11 000	None	3	60.0	5	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 5 days. recovery uneventful.
4	25 000	None	5	62.5	4	Patient afebrile in 48 hr. x-ray evidence that chest had cleared in 7 days. recovery uneventful.
5	21 400	None	5	55.8	5	Patient afebrile in 36 hr. x-ray evidence that chest had cleared in 7 days. recovery uneventful.
6	28 000	None	5	15.0* 99.0†	4 5	Patient afebrile in 72 hr. x-ray evidence that chest had cleared in 8 days. recovery uneventful.
7	16 400	None	7	60.0	5	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 7 days. recovery uneventful.
8	14 900	None	4	55.0	6	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 6 days. recovery uneventful.
9	16 900	None	4	84.0	4	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 7 days. recovery uneventful.
10	18 000	None	5	7.5* 75.0†	3 2	Persistent low temperature for 72 hr. x-ray evidence that chest had cleared in 11 days. patient afebrile 12 hr. after oral therapy.
11	15 500	None	6	85.0	5	Patient afebrile in 18 hr. x-ray evidence that chest had cleared in 7 days. recovery uneventful.
12	18 600	None	4	15.3* 82.3†	1 4	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 6 days. recovery uneventful.
13	12 200	None	4	7.5	5	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 5 days. respiratory infection on 5th day with no relapse.
14	16,600	None	3	50.0	5	Patient afebrile in 30 hr. x-ray evidence that chest had cleared in 4 days. recovery uneventful.
15	13 200	None	5	10.0* 96.0†	2 4	Patient afebrile in 50 hr. and improved rapidly after oral therapy. chest failed to clear by 6 days.
16	12 500	None	5	10.0*	5	Patient afebrile in 60 hr. slow clinical recovery. x-ray evidence of clearing in 7 days.
17	16 000	None	5	4.0* 56.0†	3 3	Persistent low fever for 6 days. good clinical response. x-ray evidence that chest had cleared in 4 days.
18	18 500	None	4	88.0	5	Patient afebrile in 18 hr. x-ray evidence that chest had cleared in 5 days. recovery uneventful.
19	26,000	None	4	7.0*	8	Blood culture showed <i>Staph. aureus</i> (hemolytic). patient afebrile in 12 hr. x-ray evidence of clearing in 5 days. recovery uneventful.
20	13 000	Penicillin sulfadiazine.	7	6.0*	10	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 9 days. recovery uneventful.
21	23,500	None	2	52.0	4	Patient afebrile in 6 hr. x-ray evidence that chest had cleared in 5 days. recovery uneventful.
22	14 600	None	5	5.4*	7	Persistent low fever for 96 hr. x-ray evidence that chest had cleared in 9 days. gradual clinical recovery.
23	21 200	None	8	5.0*	5	Patient afebrile in 12 hr. x-ray evidence that chest had cleared in 7 days. recovery uneventful.
24	10,500	None	4	4.5*	6	Patient afebrile in 36 hr. x-ray evidence that chest had cleared in 9 days. recovery uneventful.
25	25 000	None	2	75.0	10	Patient afebrile in 18 hr. x-ray evidence that chest had cleared in 7 days. recovery uneventful.
26	27 000	Penicillin	7	47.0	10	Measles with pneumonia. no clinical response in 48 hr. penicillin added with gradual improvement.
27	10 000	None	5	8.1*	4	Patient afebrile in 60 hr. x-ray evidence that chest had cleared in 4 days. recovery uneventful.
28	11 800	Sulfadiazine penicillin	8	60.0	3	Patient afebrile in 6 hr. x-ray evidence that chest had cleared in 3 days. recovery uneventful.
29	12 300	Sulfadiazine	2	5.3*	5	Patient afebrile in 48 hr. x-ray evidence that chest had cleared in 6 days. recovery uneventful.
30	9 000	Sulfadiazine	2	75.0	6	Patient afebrile in 36 hr. x-ray evidence that chest had cleared in 3 days. recovery uneventful.

prove after forty-eight hours of oral aureomycin. Penicillin and aureomycin were then given in combination, and the patient slowly improved, the temperature gradually returning to

aureomycin in this case was somewhat complicated. However, it is our impression that the drug exerted little or no salutary effect on the course of the illness.

Physical examination disclosed an acutely ill, dyspneic infant with a temperature of 104.8°F, a pulse of 200 and respirations of 120 per minute. There were coarse and crepitant rales at both bases. The white-cell count was 26,000, with 49 per cent neutrophils and a predominance of immature

The patient was placed in an oxygen tent, and aureomycin was administered intramuscularly in a dosage of 10 mg every 8 hours. The infant improved rapidly, and in 12 hours was afebrile and out of oxygen. Except for slight rises in temperature on the 2nd and 4th hospital days, recovery was un-

TABLE 3 Summary of 30 Cases of Bacterial Pneumonia Treated with Aureomycin

CASE No	PATIENT	AGE	TEMPERATURE	SEVERITY	LOCATION	NASOPHARYNGEAL CULTURE
1	S L.	yr 7	°F 103.0	Moderate	Left lower lobe	Pneumococcus, beta hemolytic streptococcus
2	S M.	1 10/12	104.0	Marked	Right (bronchopneumonia)	Pneumococcus, <i>N. catarrhalis</i>
3	H C.	7	103.4	Marked	Right upper lobe	Pneumococcus gamma streptococcus staphylococcus (nonhemolytic)
4	N H.	7	104.4	Moderate	Left lower lobe	Pneumococcus <i>N. catarrhalis</i>
5	W S.	7	104.4	Mild	Left upper lobe	Pneumococcus <i>N. catarrhalis</i> <i>H. influenzae</i>
6	G M.	8/12	104.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (hemolytic) <i>H. influenzae</i>
7	D G.	4	105.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (hemolytic)
8	J T.	3	104.0	Moderate	Right lower lobe	Pneumococcus <i>Staph. aureus</i> (hemolytic)
9	B T.	1 4/12	106.0	Mild	Right lower lobe	Pneumococcus <i>N. catarrhalis</i>
10	A C.	1 10/12	104.8	Moderate	Right upper lobe	Pneumococcus <i>N. catarrhalis</i> <i>Staph. aureus</i> (non hemolytic)
11	M P.	9/12	105.0	Marked	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (hemolytic)
12	R C.	2 4/12	103.0	Marked	Right and left (bronchopneumonia)	Pneumococcus
13	P F.	1 4/12	105.0	Moderate	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (hemolytic)
14	W S.	6	104.0	Mild	Left lower lobe	Pneumococcus
15	V B.	8/12	101.0	Marked	Right and left (bronchopneumonia)	Pneumococcus <i>Haemophilus pertussis</i> <i>Escherichia coli</i> <i>Staph. aureus</i> (nonhemolytic)
16	E J.	3/12	102.6	Marked	Right (bronchopneumonia)	Pneumococcus <i>H. pertussis</i> <i>Staph. aureus</i> (hemolytic)
17	A C.	6	103.0	Marked	Right lower lobe	Beta hemolytic streptococcus <i>N. catarrhalis</i>
18	T D.	5	102.0	Mild	Left lower lobe	Beta-hemolytic streptococcus
19	V F.	3/12	104.8	Marked	Right and left (bronchopneumonia)	Pneumococcus <i>Staph. aureus</i> (nonhemolytic)
20	V E.	9/12	101.0	Marked	Right and left (bronchopneumonia)	<i>Esch. coli</i> (hemolytic) gamma streptococcus
21	J B.	10	105.2	Marked	Right and left (bronchopneumonia)	<i>Staph. albus</i> (hemolytic) gamma streptococcus
22	G W.	2	103.4	Moderate	Right and left (bronchopneumonia)	<i>N. catarrhalis</i> <i>Staph. aureus</i> (nonhemolytic)
23	D G.	1 7/12	104.8	Moderate	Right and left (bronchopneumonia)	<i>Staph. aureus</i> (hemolytic) <i>N. catarrhalis</i>
24	B L.	2	102.4	Mild	Right lower lobe	<i>Staph. aureus</i> (hemolytic) pneumococci (few)
25	H B.	5	104.6	Mild	Right and left (bronchopneumonia)	<i>Staph. aureus</i> (hemolytic)
26	R K.	6	103.6	Marked	Right and left (bronchopneumonia)	<i>Staph. albus</i> (hemolytic)
27	W D.	5/12	103.0	Marked	Right and left (bronchopneumonia)	<i>N. catarrhalis</i> <i>H. influenzae</i> <i>Staph. albus</i> (hemolytic)
28	W T.	2	104.4	Mild	Right and left (bronchopneumonia)	<i>Staph. aureus</i> (nonhemolytic)
29	H M.	1 5/12	100.2	Marked	Right and left (bronchopneumonia)	<i>N. catarrhalis</i> <i>Staph. albus</i> (nonhemolytic)
30	D S.	6	100.4	Mild	Right (bronchopneumonia)	Gamma streptococcus

*Intramuscular injection

†Oral administration

forms. Hemolytic *Staph. aureus* was cultured from the blood, and nonhemolytic *Staph. aureus* and pneumococcus were isolated from the nasopharynx. X-ray study of the chest revealed a disseminated bronchopneumonia. The course and other data are shown in Figure 3.

eventful. Subsequent blood cultures were negative, and aureomycin was discontinued after 8 days.

The patient in the bacterial group who was considered not to have benefited by aureo-

appears some two to four weeks after the onset of the illness these procedures have diagnostic value only in retrospect.

The rationale for a trial of aureomycin in atypical viral pneumonia rests on somewhat tenuous ground in view of the lack of precise etiologic data regarding the nature of the disease. It is known that the drug is particularly effective against some viruses, principally of the psittacosis-lymphogranuloma-venereum group. However, against the viruses of influenza A and B aureomycin has been found to exert no inhibitory effect *in vitro*. With the demonstrated ineffectiveness of penicillin and sulfonamide in atypical viral pneumonia it was considered worth while to treat a series of these patients as part of our investigation of the general efficacy of aureomycin in pneumonias in children. Nine cases appeared to fall into the category of atypical viral pneumonia. In the 5 cases that fulfilled all the criteria including serologic confirmation, the age range was two and a half to eleven years. The temperatures varied from 101 to 105°F. The illness was classified as severe in 1 case, moderate in 2 and mild in 2. None of the patients required oxygen.

Nasopharyngeal cultures consistently failed to reveal any pathogens. The white-cell counts varied from 7000 to 11 000. Four of the 5 patients had cold agglutinin titers ranging from 1:64 to 1:2048, whereas the streptococcus MG titers ranged be-

bodies noted in atypical pneumonias, a drop in titer was usually observed in the bacterial group during the second and third weeks. This has been reported previously by Young.⁹

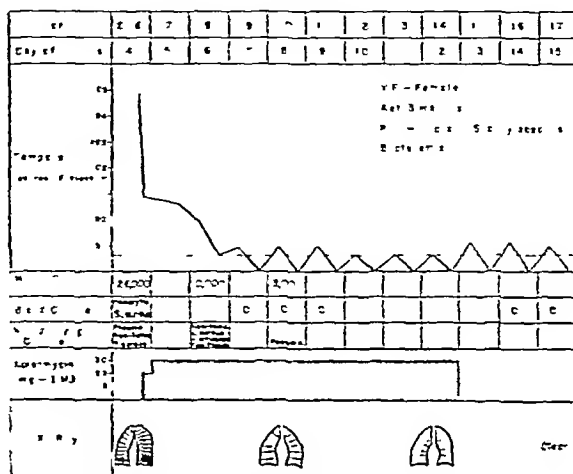


FIGURE 7. Clinical Course and Laboratory and X-Ray Findings in 1 F.

Four of the 5 patients had had previous therapy without apparent benefit. Penicillin in therapeutic doses had been tried for at least three days, and in 2 cases chemotherapy had been used in addition.

TABLE 4 (Continued)

CASE No.	MAXIMUM WHITE CELL COUNT	PREVIOUS THERAPY	AUREOMYCIN THERAPY			RESULTS
			DAY INITIATED	DOSE (kg 12 hr)	TOTAL DURATION (days)	
1	~ 900	Penicillin	9	30.0	6	Patient afebrile in 36 hr; recovery uneventful. x-ray evidence of clearing in 8 days.
2	~ 900	Penicillin sulfadiazine	~	~ 0.0	6	Patient afebrile in 36 hr; recovery uneventful. x-ray evidence of clearing in 7 days.
3	~ 700	None	4	0.0	~	Patient afebrile in 24 hr; recovery uneventful. x-ray evidence of clearing in 6 days.
4	1~ 700	Penicillin sulfadiazine	~	66.0	~	Patient afebrile 108 hr; clearing in 15 days. equivocal response. x-ray evidence of clearing in 15 days.
5	11 000	Penicillin sulfadiazine	3	0.4*	4	Patient afebrile in 18 hr; recovery uneventful. x-ray evidence of clearing in 4 days.
6	~ 100	Penicillin	4~	4~	3	Patient afebrile in 12 hr; recovery uneventful. x-ray evidence of clearing in 7 days.
7	10 000	Penicillin	3	~5	4	Patient afebrile in 24 hr; recovery uneventful. x-ray evidence of clearing in 5 days.
8	~ 700	Sulfadiazine	6	~2	~	Patient afebrile in 60 hr; recovery uneventful. x-ray evidence of clearing in 9 days.
9	6,400	None	6	60	~	Patient afebrile in 24 hr; recovery uneventful. repeat roentgenograms not taken.

tween 1:20 and 1:640. It should be pointed out that 4 patients with bacterial pneumonia had titers of cold agglutinins above 1:64 at the time of admission. However, in contrast to the rising anti-

Aureomycin therapy was instituted from four to nine days after the onset of illness. Four of the patients showed a favorable response and became afebrile thirty-six hours after therapy was started.

TREATMENT OF VIRAL PNEUMONIA

The diagnosis of primary atypical pneumonia is a difficult one, and the clinical picture, especially in infants and children, is often confusing. The

and a superimposed bacterial invader. Such cases of mixed infections are peculiarly indigenous to the pediatric age group. Furthermore, the hypothesis has been advanced by some investigators that primary atypical pneumonia may be caused by the synergistic action of bacteria and some unknown virus.⁸

Arbitrarily, the diagnosis of atypical viral pneumonia in our series was predicated on the history of cough, fever and physical and roentgenologic demonstration of pulmonary involvement, together with such laboratory aids as significant cold hemagglutination and streptococcus MG titers with normal white-cell counts. In a negative sense, the absence of pathogens from the nasopharynx as well as the lack of an adequate response to sulfadiazine or penicillin, or both, constituted additional evidence of a viral pneumonia.

Regarding the serologic phenomena associated with viral pneumonia, Horsfall⁸ reported that 55 per cent of cases will show a positive cold hemagglutination reaction in a significant titer of 1:40 or above within two to four weeks of the onset of the illness. This investigator has also shown that streptococcal MG agglutinins in titers of 1:20 or above appear within the third to the fifth week in 50 per cent of cases of viral pneumonia. Unfortunately, this investigation was performed primarily on adults. Whether infants and children show the same serologic response has not been conclusively

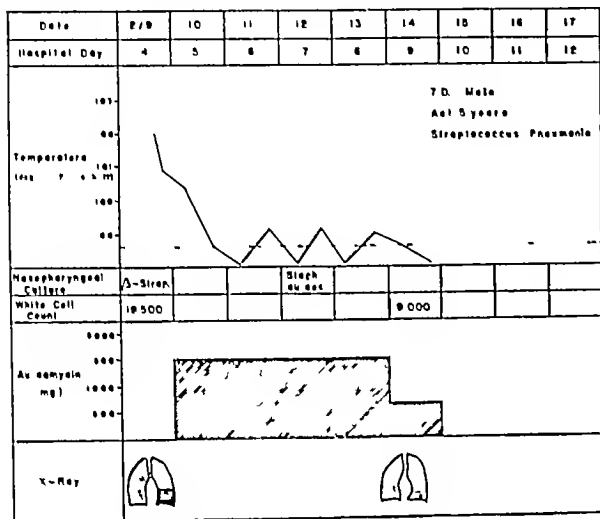


FIGURE 2. Clinical Course and Laboratory and X-Ray Findings in T. D.

disease varies widely in its clinical manifestations and severity of symptoms. The first indication that a case of pneumonia may be due to a viral agent

TABLE 4. Summary of 9 Cases of Viral Pneumonia Treated with Aureomycin

CASE No.	PATIENT	AGE	TEMPERATURE	SEVERITY	LOCATION	NASOPHARYNGEAL CULTURES	COLD AGGLUTININS	STREPTOCOCCUS MG TITERS
1	R. W.	5	102.4	Moderate	Right (bronchopneumonia)	<i>N. catarrhalis</i> <i>Staph. albus</i> (hemolytic)	1 wk -1:4 2 wk -1:128 6 wk -1:256	Negative
2	M. W.	11	101.0	Mild	Left lower lobe	<i>Staph. aureus</i> (nonhemolytic)	1 wk -1:64 3 wk -1:256 4 wk -1:128	1 wk -1:10 4 wk -1:20
3	P. M.	11	101.0	Mild	Right upper lobe	<i>Streptococcus</i> (hemolytic)	1 wk -negative 2 wk -1:64	1 wk -1:10 3 wk -1:640
4	D. L.	9	105.2	Marked	Right upper lobe	<i>Staph. aureus</i> (hemolytic) <i>Bacillus subtilis</i>	3 wk -1:2048 5 wk -1:256	5 wk -1:10 3 wk -1:40
5	I. S.	27/12	101.6	Moderate	Right (bronchopneumonia)	<i>Streptococcus</i> (nonhemolytic)	1 wk -negative 2 wk -negative	4 wk -negative
6	C. H.	4	101.0	Mild	Right and left (bronchopneumonia)	<i>Staph. albus</i> (hemolytic)	4 wk -1:16	1 wk -negative 2 wk -negative
7	D. N.	1/12	103.0	Marked	Right and left (bronchopneumonia)	<i>Staph. aureus</i> (nonhemolytic)	1 wk -1:64 2 wk -negative	1 wk -negative 2 wk -negative
8	A. B.	1	102.6	Mild	Right and left (bronchopneumonia)	<i>Staph. aureus</i> (hemolytic)	3 wk -negative	2 wk -negative 1 wk -negative
9	H. H.	3	102.4	Mild	Right and left (bronchopneumonia)	<i>N. catarrhalis</i>	1 wk -negative 2 wk -negative	1 wk -negative 2 wk -negative

*Intramuscular injection
†Oral administration

is frequently the failure to respond to antibiotics or chemotherapy. Not infrequently, the clinical picture is further complicated by the presence of a mixed infection consisting of both a viral agent

demonstrated since there is a paucity of well controlled studies in the literature. It should be noted that in view of the fact that confirmation of the diagnosis of viral pneumonia from serologic studies

agglutinins on admission were negative, however, on the 21st day of illness a titer of 1:2048 was demonstrable. Streptococcus MIG titer, which was 1:10 on admission, had risen to 1:640 on the 21st day. Roentgenograms revealed an area of homogenous density involving the entire right upper lobe. A repeat film 1 week later showed a gradual decrease in the opacity. The clinical course and other data are shown in Figure 5.

Aureomycin was started in a dosage of 500 mg every 4 hours by mouth for 3 days and was then reduced to 250 mg every 4 hours. The patient gradually improved, the temperature falling by lysis over a 5-day period with daily elevations. The toxicity subsided slowly over the same period, but on physical examination there was little change.

It is difficult to attribute any beneficial effect to aureomycin in this case. It was believed that a spontaneous remission was the more likely explanation for this child's slow improvement.

DOSAGE AND MODE OF ADMINISTRATION

Aureomycin was administered both orally and intramuscularly in this series. Oral medication alone was given to 25 patients. Nine received the drug intramuscularly, and 5 received it by both routes (but not simultaneously).

Whenever possible, the drug was administered in capsules. In the younger patients who were unable to swallow capsules the contents were emptied, and one of the following vehicles was used (depending on the likes and dislikes of the child): chocolate syrup, cherry syrup, applesauce, strained pears, lemon juice, orange juice, chocolate milk and jello. For the most part both infants and children accepted the aureomycin in spite of its disagreeable taste.

The daily dose in the patients with bacterial pneumonias who were given oral medication ranged from 40 to 100 mg per kilogram of body weight per day, with an average of 63.5 mg. The patients with viral pneumonias received 25 to 65 mg per kilogram of body weight per day, with an average of 45.5 mg. It should be pointed out that the latter group was composed largely of older children. No special attempt was made to calculate a precise dose of the drug on a weight basis. The drug was given orally in divided doses at an interval of four to six hours. The intramuscular dosage varied from 3.0 to 12.0 mg per kilogram per day, with an average of 6.5 mg, the drug being administered at eight-hour intervals.

Aureomycin exhibited no untoward reactions aside from those referable to gastrointestinal irritation. The triad of nausea, vomiting and diarrhea occurred in 2 patients, whereas occasional vomiting without diarrhea was observed in 5.

In the determination of the time that elapsed before the patients became afebrile, a significant correlation was observed between the rapidity of defervescence and the mode of drug administration. Of the 13 infants and children who received intramuscular injection of aureomycin, 4 had a temperature drop to normal in less than thirty-six hours, and the temperature in 9 became normal after thirty-

six hours. In comparison, 22 of the 26 orally treated patients had a normal temperature in less than thirty-six hours, whereas only 4 cases required more than thirty-six hours. Several of the infants treated by the intramuscular route showed tender, indurated buttocks, and this may have been a factor in the persistence of fever. It was our impression that the oral mode of administration of aureomycin was superior to the intramuscular in its clinical effect in this series, hence, the intramuscular route was discarded early in the study, and thereafter employed only when it was impossible to give the drug by mouth. It is well to point out, however, that comparable doses of the drug orally and intramuscularly were not used, and therefore any rigid comparison between the two modes of administration would be untenable. Larger doses of the drug intramuscularly were not employed primarily because of the greater severity of local reactions with increasing amounts of the drug.

SUMMARY

Aureomycin was used in the treatment of 39 cases of pneumonia in infants and children.

In the 30 cases of bacterial pneumonias treated with the drug, the results were considered good in 24, fair in 5 cases and poor in only 1. The results were particularly good in pneumococcal pneumonia. Twenty-eight of the thirty patients were afebrile within seventy-two hours of initiation of aureomycin therapy.

In the 9 cases of viral pneumonia treated with aureomycin, all but 1 case were considered to have been favorably affected by the drug although the response was somewhat less striking than that observed with bacterial pneumonia.

Aureomycin was found to be more effective clinically when given orally than when given intramuscularly.

No toxic effects were observed in this series except for the occasional occurrence of nausea, vomiting and diarrhea.

We are indebted to Sara Stevens, B.S., M.T., and Mrs. Sarah Gouge for their technical assistance, to Phyllis Allred, R.N., and Lucie Knies, R.N., for their help in the compilation of statistics and to Dr. Harold W. Bischoff for the diagrams.

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Roentgenologically, however, the pneumonic process was found to resolve more slowly than in the cases of bacterial pneumonia. The fifth patient (who is described below in detail) required four and a half days for defervescence, and this case was regarded as a probable therapeutic failure.

Four other cases were classified as having a probable viral etiology. The diagnosis in this group was based on the fact that nasopharyngeal cultures showed only nonpathogens, a leukopenia was present and the patients had failed to respond to antibiotics or chemotherapy. However, serologic tests for cold agglutinins and streptococcus MG anti-

cultured from the nasopharynx. X-ray study of the chest revealed a diffuse infiltration throughout the entire right side of the chest suggestive of bronchopneumonia and an increase in bronchovascular markings throughout the left side of the chest. The cold agglutinin titer on admission was 1:4, however, on the 18th day, it had risen to 1:128 and on the 40th day, the titer was 1:256. The clinical course and other pertinent data are shown in Figure 4.

The patient was given 300,000 units of procaine penicillin in oil intramuscularly daily for 4 days. However, the temperature remained elevated, ranging from 102 to 104°F and there was no clinical improvement. Penicillin was discontinued, and on the 4th hospital day, aureomycin therapy was instituted, 100 mg was given orally every 2 hours for three doses and then every 4 hours for a total of 5.1 gm over a period of 6 days. Twelve hours after the institution of therapy the temperature returned to normal and remained so except for a transitory elevation to 100.6°F on the following day. The child improved rapidly, and the chest findings gradually returned to normal. Roentgenologically the lesion resolved rather slowly but finally cleared within 8 days.

The patient was discharged in good condition on the 16th hospital day. He remained well at home and was found to be in good health when seen in the follow-up clinic 3 weeks later.

The case of a patient with atypical virus pneumonia who failed to respond to aureomycin was as follows:

D L, a 9-year-old girl, was admitted to the hospital with a nonproductive cough of 7 days' duration accompanied by slight anorexia but little or no fever. When she became febrile 4 days later, sulfadiazine had been started, however, her toxicity had progressed, necessitating admission to another hospital. Combined penicillin and sulfadiazine administered over a 3-day period appeared to be of little benefit, and the patient was transferred to the Children's Hospital for aureomycin therapy.

Physical examination revealed an acutely ill girl with a temperature of 105°F orally and respirations of 35 per minute. Positive findings were limited to the chest, which showed

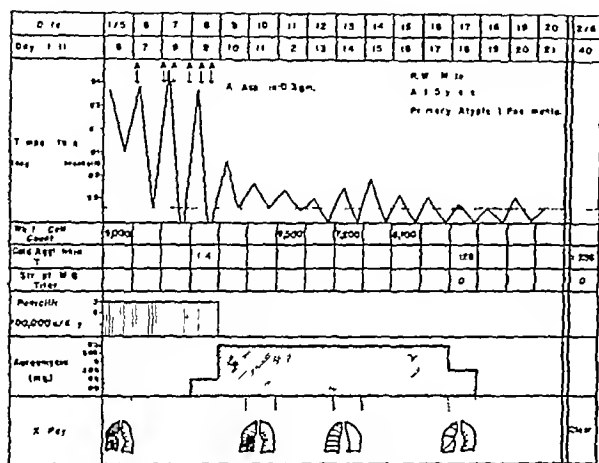


FIGURE 4 Clinical Course and Laboratory and X-Ray Findings in R W

bodies were negative. No attempts were made to isolate a viral agent. Each of these four cases showed a relatively good response to aureomycin therapy, with defervescence within thirty-six hours and clearing of the pneumonic process roentgenologically within five to eight days.

Details of the 9 cases with viral pneumonia are summarized in Table 4.

The following case is representative of the patients with atypical viral pneumonia who responded favorably.

R W, a five-year-old Negro boy, was well until 5 days before admission, when he began to cough. Two days later he began to vomit and had an elevation of temperature. These symptoms persisted until admission to the hospital.

Physical examination revealed an acutely ill boy with mild dyspnea. The temperature was 102.4°F. The tonsils were enlarged and injected. There were dullness and tubular breathing over the third to fifth interspaces anteriorly on the right, and dullness and increased breath sounds below the left scapula.

The white-cell count was 9000, with 80 per cent neutrophils. Blood cultures taken on the 1st and 2nd hospital days were sterile. A catarrhalis and hemolytic *Staph. albus* were

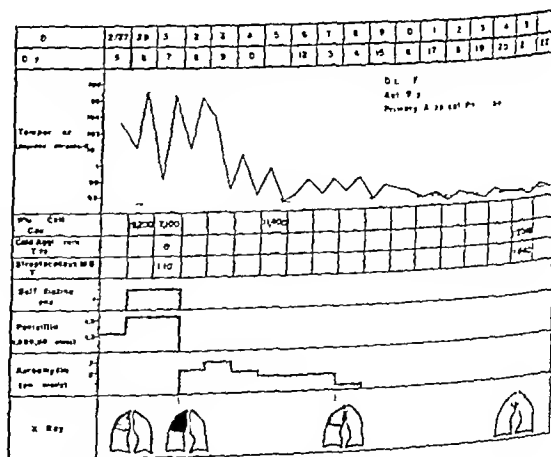


FIGURE 5 Clinical Course and Laboratory and X-Ray Findings in D L

a dullness and suppression of breath sounds over the right upper lobe.

Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 12.5 gm, and a white-cell of 7100, with 84 per cent neutrophils, 4 per cent of which were segmented. Urinalysis was essentially normal. A nasopharyngeal culture grew out hemolytic *Staph. aureus*. Cold

the midline it a severe attack was not treated promptly. Attacks were sometimes preceded by visual symptoms and were occasionally associated with nausea. Striking vascular phenomena were associated with the attack. These included generalized pallor before the headache and palpable pounding pulsation of peripheral arteries, particularly the right facial and right temporal arteries during the headache. The family history was positive for migraine and for gout.

The patient received no ergotamine tartrate until the fall of 1942. During the spring and summer of that year the frequency of migraine attacks increased from an average of one attack every 2 or 3 days until they were recurring daily. In July, 1942, an episode of status hemicranialis necessitated hospitalization. A ventriculogram performed at this time was normal. An electroencephalogram in 1942, and again in 1947, showed some minor abnormalities, more prominent on the left side (the side opposite the headache) but no localizing signs were present. Arteriography was not carried out during the 1942 admission but an arteriogram in 1947 was normal.

Figure 1 shows the average monthly requirement of ergotamine tartrate (Gynergen) required for the relief of headache from the time its use was initiated in 1942, until it was finally discontinued in 1947. When dihydroergotamine methylsulfate (DHE 45) was introduced, attempts were made to substitute this agent because of its lesser toxicity. It was found that 2 cc. (2 mg.) of dihydroergotamine could be substituted for each 1 cc. (0.5 mg.) of ergotamine, but that doses of dihydroergotamine adequate to relieve headache generally produced the same unpleasant side-effects as adequate doses of ergotamine—namely, some nausea and a single short episode of vomiting. Substitution of dihydroergotamine for ergotamine was also attempted several times during the period in which tolerance developed, and it became apparent that tolerance for the two agents was developing simultaneously and at the same rate. The headache was not relieved when 0.5 mg. of ergotamine was replaced by 0.2 mg. of ergonovine.

In the fall of 1942 when the patient first received ergotamine, the clinical response was most gratifying and was followed by a decrease in the frequency of attacks to one every 4 days. Later that year and in early 1943 attacks occurred even less often, but they increased in frequency with the return of warm weather. During the winter of 1943–1944, the patient enjoyed a 2 months' complete remission, but again the headaches recurred with warmer weather and they gradually increased in frequency and in severity.

Attacks were particularly severe during the summer of 1946. Beginning in May, 1946, headaches recurred daily. At first, they were well controlled by single daily injections of 0.5 mg. of ergotamine tartrate, but in July, 1946, larger single doses were required and the attacks recurred as frequently as twice or three times a day. Only on a single day from May, 1946, until 20 months later was headache ever completely absent. During this period and during the following months, the patient's peripheral vascular status was examined before each injection of ergotamine but no evidence of the development of peripheral vascular insufficiency was ever noted.

From July, 1946, until its use was interrupted in January, 1947, the amount of ergotamine required to control symptoms increased more or less continuously along the logarithmic curve shown in Figure 1. In the final weeks of its use, its efficacy became so slight that the administration of the required large intramuscular injections presented a real problem. Individual doses of 7 cc. (3.5 mg.) of ergotamine tartrate or of 12 cc. of dihydroergotamine methylsulfate (12.0 mg.—equivalent to 3.0 mg. of ergotamine) were given four times during the first 12 days of January, 1947, 10-cc. doses of dihydroergotamine were also given on eight occasions during this period. The largest total daily dose was given on January 10, 1947, when the patient received 13 cc. of ergotamine tartrate and 39 cc. of dihydroergotamine methylsulfate over a 24-hour period, a dosage of alkaloid equivalent to 16.5 mg. of ergotamine tartrate. During the entire month from December 12, 1946, until the use of ergot derivatives was discontinued on January 12, 1947 the patient received 531 cc. of ergotamine tartrate and 598 cc. of dihydroergotamine methylsulfate, administered intramuscularly in 115 individual doses.

Small doses of ergotamine tartrate, 0.5 mg. every 2nd or 3rd day, were again given during a period of attempted medical therapy in July and August, 1947, after external-

carotid ligations had proved unsuccessful. These doses were without effect on the headache. On October 1 a single intravenous infusion of 150 mg. of dihydroergotamine methylsulfate was given over a period of 6 hours. The procedure was uneventful for the first 5½ hours but was discontinued in the last ½ hour, when the patient complained of muscle cramps in both legs. This was accompanied by a fall in skin temperature and obliteration of the left dorsalis pedis pulse for 5 days. The left femoral and popliteal pulses were present throughout.

Since it became apparent not only that the headaches were more frequent but also that ergotamine was less effective, trials of many of the other current nonoperative treatments of migraine were undertaken. One hundred per cent oxygen gave partial relief in milder attacks but was the only agent to do so to a significant degree apart from narcotics and the

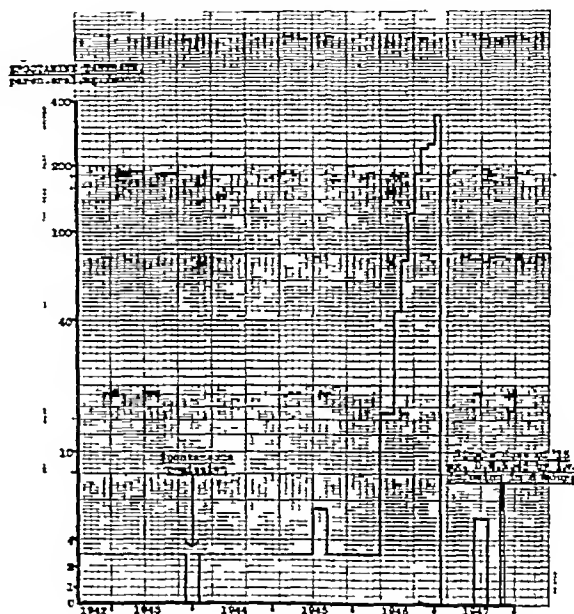


FIGURE 1 Average Monthly Requirement of Ergotamine Tartrate in a Patient with Unusually Severe Migraine

The dotted lines indicate periods for which the data are approximate. When supplementary DHE 45 (dihydroergotamine methylsulfate) was given, 4 mg. was considered the equivalent of 1 mg. of ergotamine tartrate. The dosage of 5 mg. a month in July and August, 1947, did not relieve headache.

vasoconstrictor analgesics of the ephedrine-benzedrine group. Attempts to uncover and to treat allergic hypersensitivity to histamine or environmental agents and a fifty-hour trial of psychoanalytic psychotherapy were likewise ineffective. No medical measures had any real degree of efficacy. Ligation of the right external carotid artery relieved pain partially for a short time, but the intensity of the pain began to increase 5 weeks postoperatively and soon had returned to its preoperative severity. Ligation of the left external carotid artery, ligation of the right middle meningeal artery and avulsion of the greater superficial petrosal nerve were entirely unsuccessful.

During this period, when ergotamine was losing its effectiveness, and subsequently when its use was stopped, and until the patient finally received neurosurgical relief, meperidine hydrochloride (Demerol) was required in increasing amounts to control pain, finally reaching a level of 3.0 gm. subcutaneously per day. It was discontinued without withdrawal symptoms after the pain was relieved.

The patient was completely relieved of headache by a section of the posterior root of the right trigeminal nerve performed at the Massachusetts General Hospital on December

DEVELOPMENT OF TOLERANCE TO ERGOT ALKALOIDS IN A PATIENT WITH UNUSUALLY SEVERE MIGRAINE*

WILLIAM Q. WOLFSON, M.D.† AND JOHN R. GRAHAM, M.D.‡

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ERGOTAMINE tartrate (Ginerger) and the closely related dihydroergotamine methylsulfate (DHE 45) appear to be the most successful pharmacologic agents yet proposed for the treatment of migraine attacks. Careful study of the properties and liabilities of these agents is justified by the fact that they may become irreplaceable in the treatment of very severe migraine unless the risks of narcotic addiction or intracranial surgery are to be assumed. It seems worth while, therefore, to report a case in which tolerance to these drugs developed and to describe the heroic measures that subsequently became necessary to control the patient's pain.

When properly administered in adequate dosage, early in the headache phase of the attack ergotamine tartrate will rapidly terminate the attack in from 80 to 90 per cent of patients with migraine. The mechanism of its action depends upon its capacity to constrict dilated cranial arteries.¹ Dihydroergotamine is less effective in stopping headache, probably because it is a less vigorous cranial vasoconstrictor. When these drugs were compared, from 1 to 4 mg of dihydroergotamine was required to reproduce the relief of headache offered by 0.5 mg of ergotamine tartrate. Successful therapeutic amounts of these drugs often produce unpleasant toxic side-effects, such as nausea, vomiting, general lassitude, muscle cramps and transient vascular spasms. The problem, therefore, becomes one of finding, by trial and error, a dose of ergot alkaloid that will relieve headache with as few of these undesirable sequelae as possible. A few patients who tolerate ergotamine tartrate poorly will be relieved of headache by dihydroergotamine without disabling side reactions. Since the successful action of these drugs in relieving headache depends on their power of producing prolonged constriction of particular arteries, it is obvious that they should not be used in patients already suffering from obliterative vascular disease. Reports of several cases of ergotism that have occurred in patients receiving ergotamine for the relief of itching in jaundice^{2,4} suggest that the liver plays an important role in excreting or detoxifying this substance and that the presence of liver damage is a contraindication to its use. Ergotamine tartrate

should not be employed during pregnancy because of its oxytocic effect, and although dihydroergotamine is reputed to be less powerful in this respect, it should not be used in pregnancy until more is known of its effect on man.

If the contraindications listed above are observed, there seems to be no reason why parenteral doses equivalent to 1.0 cc (0.5 mg) of ergotamine tartrate should not be given as often as every other day to patients suffering from migraine. Daily, 1.0-cc (0.5 mg) doses of ergotamine have been taken with impunity over a period of several years by a few patients,⁵ but the reports of Cleveland⁶ and Isenstead⁷ suggest that, with doses of this frequency and amount, ergotism may possibly arise in otherwise healthy patients. Thus, if the daily administration of ergot derivatives becomes necessary, the patient should be forewarned and followed closely by the physician.

The minimum dose of ergotamine adequate to relieve headache, when once determined, ordinarily remains approximately constant from year to year even when the course of the disease requires frequently repeated administration. A patient of one of us has, for example, received ergotamine parenterally on an average of twelve to fifteen times each month over the past ten years. In 1938, this patient required 0.4 mg of ergotamine to relieve each migraine attack, but in 1948, 0.25 mg was equally effective although the headaches, if left untreated, apparently were not less severe. The unpleasant side-effects likewise usually remained just as active with the passage of time as they were with the first few doses. Most migraine sufferers, therefore, may count on the effectiveness both therapeutic and toxic, of ergot derivatives through the years.

In the case reported below, tolerance to both the therapeutic and toxic effects of ergotamine tartrate and dihydroergotamine methylsulfate developed rapidly after a long period of satisfactory response to normal dosage. The loss of effectiveness of these agents and the relative ineffectiveness of other medical measures, ultimately necessitated neurosurgical intervention to control pain. This appears to be the first reported case in which tolerance to ergot derivatives has developed.

CASE REPORT

A young woman had been in good health apart from severe migraine which had its onset in 1938 at the age of 20. The headache was right sided on all occasions, no headaches originated on the left side, although the pain spread across

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the midline if a severe attack was not treated promptly. Attacks were sometimes preceded by visual symptoms and were occasionally associated with nausea. Striking vascular phenomena were associated with the attack. These included generalized pallor before the headache and palpable pounding pulsation of peripheral arteries particularly the right facial and right temporal arteries, during the headache. The family history was positive for migraine and for gout.

The patient received no ergotamine tartrate until the fall of 1942. During the spring and summer of that year the frequency of migraine attacks increased from an average of one attack every 2 or 3 days until they were recurring daily. In July, 1942, an episode of status hemicranialis necessitated hospitalization. A ventriculogram performed at this time was normal. An electroencephalogram in 1942, and again in 1947, showed some minor abnormalities, more prominent on the left side (the side opposite the headache) but no localizing signs were present. Arteriography was not carried out during the 1942 admission but an arteriogram in 1947 was normal.

Figure 1 shows the average monthly requirement of ergotamine tartrate (Givnergen) required for the relief of headache from the time its use was initiated in 1942, until it was finally discontinued in 1947. When dihydroergotamine methylsulfate (DHE 45) was introduced, attempts were made to substitute this agent because of its lesser toxicity. It was found that 2 cc (2 mg) of dihydroergotamine could be substituted for each 1 cc (0.5 mg) of ergotamine, but that doses of dihydroergotamine adequate to relieve headache generally produced the same unpleasant side-effects as adequate doses of ergotamine—namely, some nausea and a single short episode of vomiting. Substitution of dihydroergotamine for ergotamine was also attempted several times during the period in which tolerance developed, and it became apparent that tolerance for the two agents was developing simultaneously and at the same rate. The headache was not relieved when 0.5 mg of ergotamine was replaced by 0.2 mg of ergonovine.

In the fall of 1942, when the patient first received ergotamine, the clinical response was most gratifying, and was followed by a decrease in the frequency of attacks to one every 4 days. Later that year and in early 1943, attacks occurred even less often but they increased in frequency with the return of warm weather. During the winter of 1943-1944, the patient enjoyed a 2 months' complete remission but again the headaches recurred with warmer weather and they gradually increased in frequency and in severity.

Attacks were particularly severe during the summer of 1946. Beginning in May, 1946, headaches recurred daily. At first, they were well controlled by single daily injections of 0.5 mg of ergotamine tartrate, but in July, 1946, larger single doses were required and the attacks recurred as frequently as twice or three times a day. Only on a single day from May, 1946, until 20 months later was headache ever completely absent. During this period and during the following months the patient's peripheral vascular status was examined before each injection of ergotamine, but no evidence of the development of peripheral vascular insufficiency was ever noted.

From July, 1946, until its use was interrupted in January, 1947, the amount of ergotamine required to control symptoms increased more or less continuously along the logarithmic curve shown in Figure 1. In the final weeks of its use, its efficacy became so slight that the administration of the required large intramuscular injections presented a real problem. Individual doses of 7 cc (3.5 mg) of ergotamine tartrate or of 12 cc of dihydroergotamine methylsulfate (12.0 mg—equivalent to 3.0 mg of ergotamine) were given four times during the first 12 days of January, 1947, 10-cc. doses of dihydroergotamine were also given on eight occasions during this period. The largest total daily dose was given on January 10, 1947, when the patient received 15 cc of ergotamine tartrate and 39 cc of dihydroergotamine methylsulfate over a 24-hour period a dosage of alkaloid equivalent to 16 mg of ergotamine tartrate. During the entire month from December 12, 1946, until the use of ergot derivatives was discontinued on January 12, 1947 the patient received 351 cc. of ergotamine tartrate and 398 cc of dihydroergotamine methylsulfate, administered intramuscularly in 115 individual doses.

Small doses of ergotamine tartrate, 0.5 mg every 2nd or 3rd day, were again given during a period of attempted medical therapy in July and August, 1947, after external-

carotid ligations had proved unsuccessful. These doses were without effect on the headache. On October 1 a single intravenous infusion of 150 mg of dihydroergotamine methylsulfate was given over a period of 6 hours. The procedure was uneventful for the first 5½ hours but was discontinued in the last ½ hour, when the patient complained of muscle cramps in both legs. This was accompanied by a fall in skin temperature and obliteration of the left dorsalis pedis pulse for 3 days. The left femoral and popliteal pulses were present throughout.

Since it became apparent not only that the headaches were more frequent but also that ergotamine was less effective, trials of many of the other current nonoperative treatments of migraine were undertaken. One hundred per cent oxygen gave partial relief in milder attacks but was the only agent to do so to a significant degree apart from narcotics and the

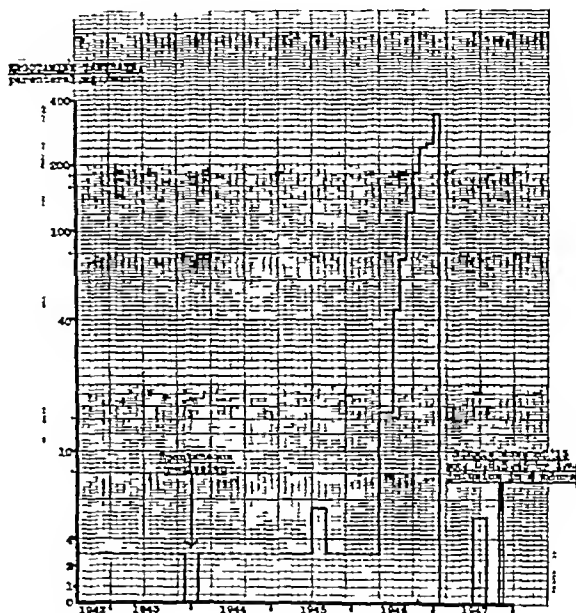


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During this period, when ergotamine was losing its effectiveness, and subsequently when its use was stopped, and until the patient finally received neurosurgical relief, meperidine hydrochloride (Demerol) was required in increasing amounts to control pain, finally reaching a level of 3.0 gm subcutaneously per day. It was discontinued without withdrawal symptoms after the pain was relieved.

The patient was completely relieved of headache by a section of the posterior root of the right trigeminal nerve performed at the Massachusetts General Hospital on December

23, 1947, by Dr James C White. At the time of writing, she has been completely free of headache for over a year.

DISCUSSION

In the case reported above, a striking resistance to large doses of ergotamine tartrate developed. During the development of this refractory state, resistance to other ergot alkaloids occurred. Thus, at various points during the phase of developing tolerance, it was possible to show, by substitution of dihydroergotamine methylsulfate for ergotamine tartrate in a ratio of 4 mg to 1 mg, that dihydroergotamine was equally effective (or, later, ineffective). Under these conditions, dihydroergotamine did not appear significantly more or less toxic than ergotamine. A number of trials with ergonovine maleate showed that refractoriness extended to this substance as well.

Resistance to the toxic effects of ergotamine appeared to develop at a rate parallel to that at which resistance to the therapeutic action developed, which suggested that the drug was being inactivated rather than that the cranial arteries were becoming refractory. At all times, the dose of ergotamine or of dihydroergotamine necessary to relieve headache also induced some nausea and usually a brief episode of sudden vomiting. If the dose given was insufficient to relieve headache, nausea and vomiting generally did not occur.

It is not clear whether interruption of the use of ergot derivatives in January, 1947, was followed by any significant return of sensitivity. Certainly, normal sensitivity did not return, as shown by the ineffectiveness of 0.5 mg of ergotamine given every two or three days during the following summer. The vascular effects of the large dihydroergotamine methylsulfate infusion of October 1, 1947, suggest that there had been some return of sensitivity. This must have been slight, however, since the infusion was tolerated at a rate of 2.5 mg per hour for over five hours before any effects were noted.

SUMMARY

What appears to be the first reported case of the development of tolerance to ergot alkaloids by a patient with migraine is reported. After three and a half years of typically satisfactory clinical response to the usual doses of ergotamine tartrate, tolerance to this agent developed rapidly and extended to dihydroergotamine methylsulfate and to ergonovine maleate as well. Refractoriness to the emetic and vascular effects of these agents developed concurrently with tolerance to the therapeutic effect. Withdrawal was not followed by a return of normal sensitivity within nine months.

During the period in which tolerance developed, most other medical measures currently used in the treatment of migraine were given trials. None were significantly successful. Surgical section of both external carotid arteries, of the right middle meningeal and right temporal arteries and of the right greater superficial petrosal nerve were ineffective. Complete relief of headache was finally obtained by surgical section of the posterior root of the right trigeminal nerve.

We are indebted to Drs Walter C Alvarez, James C White and J H Means, who kindly reviewed the manuscript, and to Dr C Henze and Mr S M Fossel, of the Sandoz Chemical Works, New York City, who generously co-operated by supplying a large part of the dihydroergotamine methylsulfate used in the study of comparative resistance to various ergot derivatives.

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LOCALIZED PRETIBIAL MYXEDEMA*

A Stigma of Hyperthyroidism

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WEST ROXBURY, MASSACHUSETTS

THE term "myxedema" is frequently used as a synonym for "hypothyroidism." It is a matter of common experience, however, that the majority of patients with clinical hypothyroidism do not have either local or generalized mucinous changes in the skin. Local myxedema in euthyroid persons is a familiar entity to the dermatologist. Such lesions usually are not symmetrically placed and appear singly or multiply on the upper or lower extremities or on the trunk. Definite, local, myxedematous changes may also occur in patients with exophthalmic goiter. A few reviews¹⁻⁴ and scattered case reports⁵⁻²⁴ have appeared. The concurrence of hyperthyroidism and local myxedema is not coincidental since all reported cases have this association. When local circumscribed lesions of myxedema have been described in hyperthyroid patients, they have, with rare exceptions, always been bilateral on the lower legs.

The gross appearance of the skin lesion is characteristic. Elevated plaques or nodules of thickened skin are present, well demarcated from the surrounding normal skin. The involved area is darker than that around it and is often yellowish pink. The hair follicles are wide and deep, producing a "pigskin" appearance. On palpation, the lesion is firm and cool, and it does not pit on pressure. Although the anterior tibial regions are always involved, extensive lesions may surround the lower leg. Symptoms arising from these areas are few. Mild, tingling pruritus or numbness may occur. Patients often complain of the unsightliness of their legs. If a biopsy is made, clear white viscous material escapes from the incision.

Histologic section reveals little change in the epidermis. In the corium the fibroelastic tissues separate into individual strands between which is a homogeneous, mucin-staining material. Occasional spindle cells are seen in this matrix. Lymphocytic infiltration around some of the smaller blood vessels is present. Pillsbury and Stokes⁶ examined all types of local myxedema and found them histologically indistinguishable. Watson² used hyaluronidase to incubate biopsied skin in his 2 cases. He obtained equimolar fractions of two polysaccharides and concluded that the mucinous material was hyaluronic

acid, chondroitin sulfuric acid or mucotin sulfuric acid. He ran similar tests on normal pretibial skin and found much less of this substance.

The lesion appears at variable times, either concurrently with the developing exophthalmos and other thyrotoxic signs and symptoms or after incomplete ablation of the toxic thyroid gland. Hyperthyroidism may be recurrent. In 69 cases reviewed by Trotter and Eden¹ the lesions appeared before treatment of the hyperthyroidism in 32, after x-ray therapy in 2 and after subtotal thyroidectomy in 35. Of the last group, 11 first showed the skin lesion during a recurrence of thyrotoxicosis. In 3 cases reported by Nettetton and Mulvey⁷ lesions developed with a recurrence of thyrotoxicosis after operation—2 during postoperative hypothyroidism and 1 sixteen years after a second thyroid operation. In a collection of isolated case reports most lesions appeared either preoperatively or with the reappearance of toxicity after partial resection.

Once present, local pretibial myxedema runs a slow and unpredictable course. Dunhill⁸ saw clearing of the lesions in 6 of his 7 cases after partial thyroidectomy, but this has not been the experience of others. The established lesion is not influenced by thyroidectomy, iodine or thiouracil derivatives. Complete remissions, without evidence of change in thyroid status, occur in some cases. Excision of the involved skin was performed occasionally for a cosmetic effect.⁶ In all cases in which the status of the eyes was mentioned, exophthalmos had been present at some time.

The incidence of this syndrome cannot be stated with less than 100 cases reported. Trotter and Eden¹ found it in 3 per cent of 130 cases of hyperthyroidism. Isolated short case reports have recently appeared,¹¹⁻²⁴ most of them as a part of the proceedings of meetings of dermatologic societies that are not listed in the *Quarterly Cumulative Index Medicus*.

Various terminologies have been suggested. Cohen,⁴ in a recent review, proposed the term "myxedema circumscriptum thyrotoxicum." This suggests that the syndrome is a definite entity and indicates its nature.

CASE REPORT

H. I. B., a 27-year-old married Navy veteran, apparently well until October, 1945, had noted gradual onset of increased perspiration, progressive loss of weight, voracious appetite, emotional lability and prominence of the eyes. He continued to sleep well, had no gastrointestinal disturbances and carried

*From the Medical Service, Veterans Administration Hospital. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author.

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23, 1947, by Dr James C White. At the time of writing, she has been completely free of headache for over a year.

DISCUSSION

In the case reported above, a striking resistance to large doses of ergotamine tartrate developed. During the development of this refractory state, resistance to other ergot alkaloids occurred. Thus, at various points during the phase of developing tolerance, it was possible to show, by substitution of dihydroergotamine methylsulfate for ergotamine tartrate in a ratio of 4 mg to 1 mg, that dihydroergotamine was equally effective (or, later, ineffective). Under these conditions, dihydroergotamine did not appear significantly more or less toxic than ergotamine. A number of trials with ergonovine maleate showed that refractoriness extended to this substance as well.

Resistance to the toxic effects of ergotamine appeared to develop at a rate parallel to that at which resistance to the therapeutic action developed, which suggested that the drug was being inactivated rather than that the cranial arteries were becoming refractory. At all times, the dose of ergotamine or of dihydroergotamine necessary to relieve headache also induced some nausea and usually a brief episode of sudden vomiting. If the dose given was insufficient to relieve headache, nausea and vomiting generally did not occur.

It is not clear whether interruption of the use of ergot derivatives in January, 1947, was followed by any significant return of sensitivity. Certainly, normal sensitivity did not return, as shown by the ineffectiveness of 0.5 mg of ergotamine given every two or three days during the following summer. The vascular effects of the large dihydroergotamine methylsulfate infusion of October 1, 1947, suggest that there had been some return of sensitivity. This must have been slight, however, since the infusion was tolerated at a rate of 2.5 mg per hour for over five hours before any effects were noted.

SUMMARY

What appears to be the first reported case of the development of tolerance to ergot alkaloids by a patient with migraine is reported. After three and a half years of typically satisfactory clinical response to the usual doses of ergotamine tartrate, tolerance to this agent developed rapidly and extended to dihydroergotamine methylsulfate and to ergonovine maleate as well. Refractoriness to the emetic and vascular effects of these agents developed concurrently with tolerance to the therapeutic effect. Withdrawal was not followed by a return of normal sensitivity within nine months.

During the period in which tolerance developed, most other medical measures currently used in the treatment of migraine were given trials. None were significantly successful. Surgical section of both external carotid arteries, of the right middle meningeal and right temporal arteries and of the right greater superficial petrosal nerve were ineffective. Complete relief of headache was finally obtained by surgical section of the posterior root of the right trigeminal nerve.

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being increased in a few days to 300 mg a day. The basal metabolic rate steadily declined from +43 to +4 per cent in 30 days. During this period the patient underwent complete remission of all symptoms except those related to his exophthalmos and the pretibial myxedema. He gained weight



FIGURE 3 Extreme Exophthalmos of the Patient Whose Skin Lesions Are Illustrated in Figure 1. At the time the photograph was taken all other signs of thyrotoxicosis were well controlled with propylthiouracil.

regularly and was permitted to return to his on-the-job training as a color matcher in a paint factory. No changes in the eyes or in the leg lesions were noted at a follow-up examination 6 months later.

SUMMARY

The syndrome of exophthalmic goiter and bilateral pretibial myxedema is a distinct entity. This distribution of local myxedema is seen only in patients with past or present thyrotoxicosis. Histologically such skin lesions are indistinguishable from other types of myxedema.

A typical case of the syndrome is reported.

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on with his duties. By late December he had lost 38 pounds of weight and was aware of a rapid heart beat. Examination at that time revealed an enlarged thyroid gland and the presence of exophthalmos. The basal metabolic rate was +55 per cent. The patient was started on Lugol's solution and was flown to the United States for definitive treatment. When his basal metabolic rate had fallen to +14 per cent a subtotal thyroidectomy was performed. The postoperative course was

for several weeks. The basal metabolic rate fell to +14 per cent but the drug was omitted because of a blood smear, which showed fewer than 50 neutrophils per cubic millimeter. For this reason the patient was admitted to the Veterans Administration Hospital in April, 1948.

Physical examination revealed a well developed and well nourished man in no distress but restless, constantly moving his hands and body. Under the right sternomastoid muscle was a firm mass, 5 by 5 cm., which moved with swallowing and appeared to be thyroid tissue. No thyroid gland was palpated on the left. Marked bilateral exophthalmos was present (Fig 3), and the lids could not be closed. Pupillary reaction was normal, and fundoscopic examination was negative. The heart was not enlarged, a regular sinus rhythm and a soft apical blowing systolic murmur were present. A fine tremor of the outstretched fingers was noted. Over each shin (Fig 1) were raised plaques, sharply demarcated, erythematous but not pitting. The hair follicles were wide and deep, the skin elsewhere was normal.

The blood pressure was 120/84, with a moderate tachycardia.

The blood serologic findings were negative, and a complete blood count was normal. The total serum cholesterol was

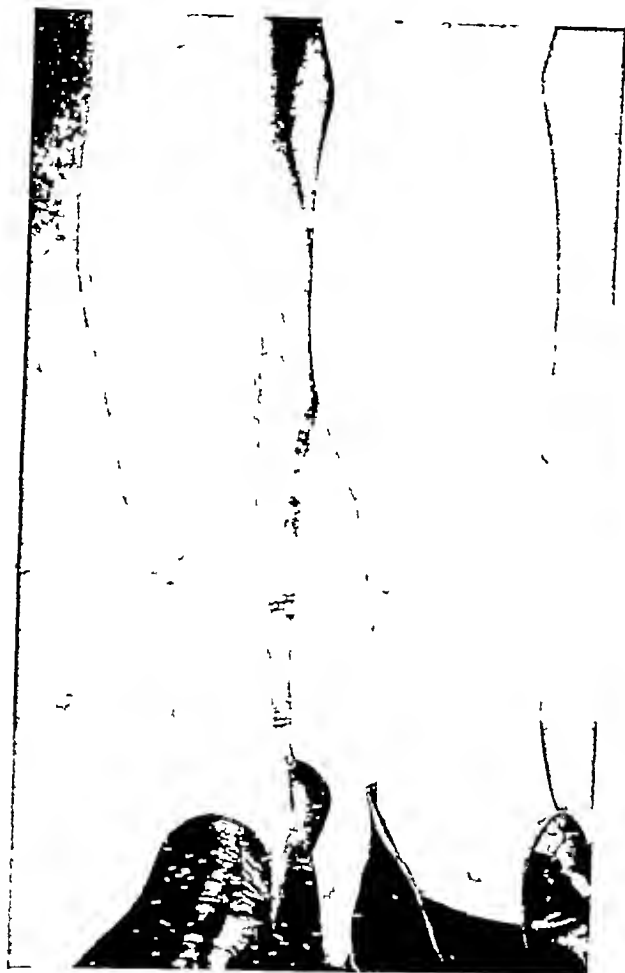


FIGURE 1 Lesions of Circumscribed Pretibial Myxedema

stormy. For several weeks he lost the sight of his right eye and had much impaired vision of the left. Although the eyes became exceedingly prominent he had no pain. Gradually the eyesight returned to its previous value, but exophthalmos continued. In March, 1946, he was sent East with the basal metabolic rate at +6 per cent. During the next 14 months he convalesced at the United States Naval Hospital at Chelsea, Massachusetts. There was a complete remission of all toxic symptoms, except exophthalmos, and he was discharged from the service.

At the time of his transfer to Chelsea the patient first noticed elevated, pink, painless areas of skin over the shins (Fig 1). They gradually increased in area but changed little if any in the months prior to admission to the Veterans Administration Hospital. A biopsy of one of the skin lesions was made at the Naval Hospital and reported as showing typical myxedema (Fig 2).

In the fall of 1947 the patient noted a return of his former toxic symptoms, including a weight loss of 14 pounds despite a large appetite. The basal metabolic rate at this time was +37 per cent. He was given propylthiouracil, 100 mg a day,

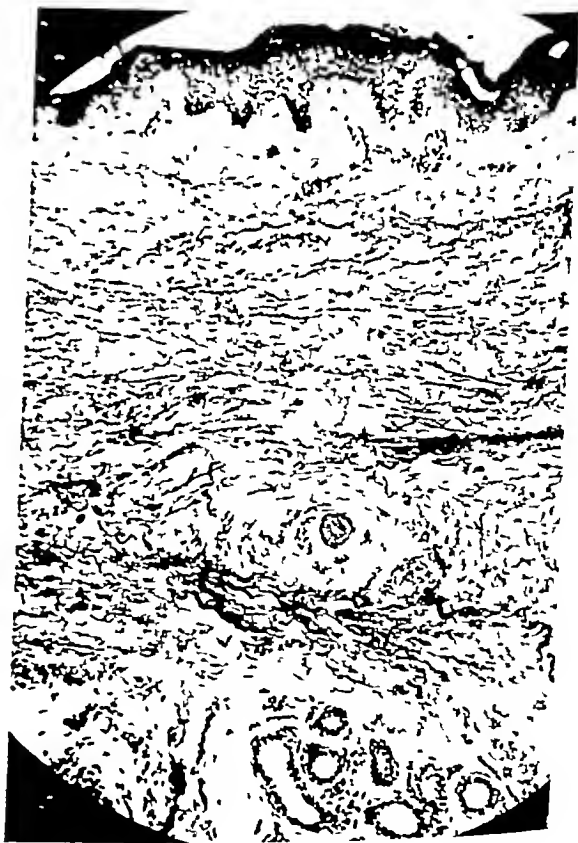


FIGURE 2 Photomicrograph of a Skin Biopsy Taken from a Pretibial Lesion of the Same Patient (The Slide was Kindly Lent for this Purpose by the United States Naval Hospital, Chelsea, Massachusetts)

161 mg, with esters of 73 mg per centimeter. A urinalysis was negative, with a specific gravity of 1.030. Subsequent white-cell counts were 7900 and 8400, with 65 per cent and 55 per cent neutrophils respectively. X-ray examination of the chest was negative. An electrocardiogram was normal except for low T waves in Lead V₆.

The patient remained afebrile. After preliminary studies he was given 200 mg of propylthiouracil a day, the dosage

SUMMARY AND CONCLUSION

Formulas before and after bacterial contamination were tested by four methods of processing

Steam pressure at 15 lb for five minutes gave adequate protection in all cases but demonstrated

TABLE 3 *Flowing-Steam-Disinfection Method — 212°F for Thirty Minutes**

COLONIES BEFORE PROCESSING per cc	COLONIES AFTER PROCESSING per cc
Evaporated milk formula Not tested	0†—0‡
Contaminated specimen (<i>Esch. coli</i> and hemolytic streptococcus) 582,000	0†—230‡ (no pathogenic organisms)
Modified 2 per cent milk formula Not tested	0†—0‡

*No coagulum formed, and the nipple shields did not become adherent to the nipples

†After 1 hr of cooling and 24 hr of refrigeration.

‡After 3 hr of cooling and 24 hr of refrigeration.

clearly the practical disadvantage by the formation of a thick coagulum with the subsequent plugging of nipple holes and the adhesion of the nipple to the paper nipple covers

Steam pressure of 6 pounds for ten minutes gave exactly the same result

Flowing steam for thirty minutes at 212°F gave adequate protection even of grossly contaminated

formulas provided refrigeration was begun within an hour of processing Moreover, no coagulation formed

Flowing steam at 180 to 200°F for fifteen minutes did not guarantee bacterial safety of the formulas

It is therefore concluded that flowing steam for thirty minutes at 212°F, since it provided a safe

TABLE 4 *Flowing-Steam-Disinfection Method — 180 to 200°F. for Fifteen Minutes*

COLONIES BEFORE PROCESSING per cc	COLONIES AFTER PROCESSING per cc
Evaporated-milk formula Not tested	0*—3*0†
Contaminated specimen (<i>Esch. coli</i> , <i>Proteus vulgaris</i> and hemolytic strep o- coccus) 295,000	10,000†
Modified 2 per cent milk formula 20,000	1900†

*Immediately after processing

†After 1 to 3 hr of cooling and 24 hr of refrigeration.

product bacteriologically and did not cause the disadvantage of a coagulum is the method of choice.

We are indebted to Drs Clement A Smith and Stewart H. Clifford for their advice and help

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MEDICAL PROGRESS

GASTROINTESTINAL ALLERGY*

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GASTROINTESTINAL allergy is a diagnosis frequently entertained occasionally evaluated and rarely established It offers to its enthusiastic supporters, a reasonable explanation for many obscure abdominal complaints To the skeptical, it frequently appears as a specious and unwarranted diagnosis Although these conflicting views cannot be resolved on the basis of existing knowledge, the present status of gastrointestinal allergy is examined in this review with the hope of separating the well founded from the hypothetical

The term includes reactions occurring in the sensitized gastrointestinal tract as a result of contact with an allergen, whether the allergen is an ingested food or reaches the gut after inhalation or injection

Although foods are considered to be the most important cause of such reactions food allergy should be distinguished from gastrointestinal allergy Food allergy includes any allergic reaction due to an ingested food, whether the reacting site is in the gut or elsewhere

The number of gastrointestinal complaints that have been ascribed to allergy make up a formidable list, which includes heartburn, epigastric pressure, fullness, bloating, belching, nausea, vomiting, distention, aches, cramps and colics, constipation, diarrhea, fecal mucus, blood in stools and even jaundice¹⁻³ Allergy has also been suggested, at one time or another, as a cause of nearly all gastrointestinal diseases of obscure origin, particularly peptic ulcer⁴ and ulcerative colitis⁵⁻⁷ To summarize each of the articles supporting allergy as a cause of gastrointestinal disorders would present the reader with a tedious sequence of detail that, red

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COMPARATIVE STUDY OF FORMULA PROCESSING FOR OBSTETRIC NURSERIES*

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OUTBREAKS of diarrhea of the newborn in hospital nurseries have in recent years caused a great deal of needed emphasis on improving the technic of nursery care and of formula preparation. To study this entire problem the American Academy of Pediatrics set up a committee on the fetus and newborn infant, and this committee has in turn created subcommittees in various states.

The committee for Massachusetts¹ made specific recommendation taken from the New York Sanitary

its advance toward the maximum. Exposure continues for 15 minutes, no longer, after which the steam is turned off and the door opened immediately. The usual 15-17 pounds pressure should be maintained in the jacket of the sterilizer.

Step 2 Remove formulas from sterilizer and allow to cool at room temperature for approximately one to two hours. Finally, transfer formulas to refrigerator maintained at a temperature of 20° to 36°F where they remain until feeding time.

Since this procedure was at variance with the recommendation of the Massachusetts Committee on the Fetus and Newborn Infant, a question was raised about the future policy of the hospital regarding formula processing. It was consequently decided that a comparative study be made of the three alternative methods suggested by the Committee and the method directed by the American Sterilizer Company.

Two types of formula were tested, both of which were in current use in the hospital. One consisted of commercial evaporated milk, karo and water, and the other was identical except for the substitution of Grade A milk with 2 per cent fat content. These two formulas were tested in all four ways, both before and after contamination with pathogenic organisms. The bacterial counts were made according to the standard "American method" for milk analysis. Transplants were made in suitable

TABLE 1 Pressure-Steam-Disinfection Method—15 lb for Five Minutes*

COLONIES BEFORE PROCESSING per cc	COLONIES AFTER PROCESSING per cc
Evaporated milk formula	
29 000	0†
48 000	0‡
38 000	0§
Contaminated specimen (<i>Escherichia coli</i> and hemolytic streptococcus)	
310 000	0†
	120‡
Modified 2 per cent milk formula	
34 000	0†—0‡—0§

*In all cases a thick coagulum formed in the formulas and the nipple shields became adherent to the nipples.

†After immediate refrigeration for 24 hr.

‡After 1 hr of cooling and 24 hr of refrigeration.

§After 3 hr of cooling and 24 hr of refrigeration.

Code for the guidance of hospitals in formula preparation. This recommendation is as follows:

Formulae and other fluids offered to newborn infants in hospitals or child caring institutions, or in maternity hospitals or maternity homes shall be poured into individual feeding bottles at the time of preparation, and a nipple shall be attached to each bottle and covered with a cap. The entire product shall be then subjected to terminal heating by steam under pressure at not less than 15 pounds for not less than 5 minutes, or at a pressure of not less than 6 pounds for not less than 10 minutes, or by flowing steam at a temperature of not less than 100°C (212°F) for not less than 30 minutes.

At the time this recommendation appeared, the hospital where the studies given below were made, was preparing the formulas in accordance with the directions published by the American Sterilizer Company,² whose apparatus³ the hospital was using. These directions were as follows:

Terminal Disinfection of Formulas

Step 1 Following preparation, the formulas are immediately placed in sterilizer and disinfected by non-pressure steam for 15 minutes at 180°-200°F. The period of exposure is timed when the thermometer indicated 180°F in

TABLE 2 Pressure-Steam-Disinfection Method—6 lb for Ten Minutes*

COLONIES BEFORE PROCESSING per cc	COLONIES AFTER PROCESSING per cc
Evaporated milk formula	
38,000	0†—0‡—0§
Contaminated specimen (<i>E. coli</i> and hemolytic streptococcus)	
380 000	0†—0‡
Modified 2 per cent milk formula	
17 000	0†—0‡—0§

*In all cases a thick coagulum also formed in the formulas and the nipple shields became adherent to the nipples.

†After immediate refrigeration for 24 hr.

‡After 1 hr of cooling and 24 hr of refrigeration.

§After 3 hr of cooling and 24 hr of refrigeration.

mediums (endo and blood agar) to test survival of pathogenic organisms added to the formulas before processing. The results of these tests are shown in Table 1-4.

For the sake of brevity in these tables only average results are shown. In all, 97 different observations were made with a minimum of 3 readings in any given test. In the tests summarized in Table 1-3 utensils were clean but not sterile. In the procedure summarized in Table 4 utensils and containers were sterilized.

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§Formula sterilizer-disinfector—cylindrical (open mounted steam heat).

CLINICAL OBSERVATIONS

Since gastrointestinal allergy includes a wide variety of complaints and exhibits no characteristic syndrome, the diagnosis cannot be made on the basis of symptoms *per se*. The majority of those who believe in the prevalence of gastrointestinal allergy consequently depend upon an apparent relation between the ingestion of a suspected food and the subsequent onset of symptoms. To some, the patient's say-so is sufficient. Thus, Andresen² believes that many medical mistakes have been made when the physician ignores a patient's observation that his symptoms follow the ingestion of certain foods, and in studying the chronology of allergic symptoms Alvarez and Hinshaw¹⁵ considered it sufficient to select their subjects on the basis that these patients "knew that the ingestion of certain foods regularly caused distress." In the opinion of others,^{19,22} the patient's incrimination of specific foods must be accepted with caution.

Even if the patient has correctly identified a certain food as the cause of his gastrointestinal symptoms, this correlation does not prove the existence of gastrointestinal allergy. Food intolerances of other origin must be considered.²⁰ Assuming that allergy does play a role, the gastrointestinal manifestations are not necessarily primary but could conceivably stem from an allergic reaction taking place elsewhere in the body. For example, gastrointestinal symptoms of all types might be caused by the intensely disagreeable sensations associated with the induction of severe asthma following the ingestion of certain foods.²³

Corroboration of impressions gained from the patient's history is frequently sought by the giving or withholding of the suspected food. If symptoms are invariably precipitated when a certain food is eaten, or conversely if they disappear on elimination diets, the culpability of the food seems to be demonstrated. Procedures of this type have consequently been used in many clinical studies that have attempted to establish the diagnosis of gastrointestinal allergy. Although the rationale of various elimination or provocative diets is similar, the technics of applying these measures vary in the hands of different allergists. The details of dietary tests are well expounded in the writings of Rowe,²² Vaughan,²⁴ Randolph,²⁵ and Rinkel.²⁶

Three major difficulties beset the diagnosis of gastrointestinal allergy as made by correlating symptoms with the eating of certain foods. In the first place, any patient's response is influenced by subjective attitudes that are difficult to exclude. Secondly, the attributes of gastrointestinal allergy are so all-inclusive that it emerges as a hazy entity with ill defined margins. Finally, neither the execution nor the interpretation of dietary tests is easy. These difficulties may now be considered in more detail.

Many physicians, aware of the emotional and situational forces that condition man's attitude toward food, accept the patient's incrimination of specific foods with reservation. Representing this point of view, Metzger²⁷ writes "If a fear or fixed idea concerning roses or goldenrod can, and apparently does precipitate a condition which is or resembles hay fever, why then is it not logical to assume that definite fears of needles, milk, and a host of other things react in the same way?" Phobias and fixed ideas are common in the neurotic." Results obtained by elimination or provocative diets may also be compromised by uncontrolled factors. Precipitation of symptoms by administration of a food to which the patient believes himself sensitive involves psychic factors sufficiently powerful to complicate the whole test. The dominant influence that such factors may exert has been demonstrated by Wolf²⁸ who showed that even the well established pharmacologic effects of a drug like atropine can be inhibited or reversed by the patient's attitude and expectations. Similarly, the apparent success of an elimination diet is hard to differentiate from the success any regimen may enjoy in the treatment of functional disorders, particularly if the regimen embodies considerable dietetic ritual and is administered by an enthusiastic physician who obviously has the patient's welfare at heart.

A fair evaluation of the effect of elimination diets in the therapy of organic disease poses comparable difficulties. In treating chronic ulcerative colitis, for example, careful observers^{6,7} insist upon removing from the diet foods that they believe play an allergenic and etiologic role. In their opinion, milk is a prime offender. Yet equally experienced physicians do not hesitate to use milk as a staple in their dietary management of ulcerative colitis. As long as ulcerative colitis remains a disease of obscure etiology, responding with approximately equal but incomplete success to a number of conflicting regimens, the etiologic implication of any therapeutic principle must be accepted with caution unless a specific relation between treatment and response is undeniable. For similar reasons, the beneficial effects claimed for elimination diets in the treatment of peptic ulcer^{4,9} are hard to evaluate.

When testing patients with foods to which sensitivity is suspected, one may reduce psychic factors by giving the test substance under carefully controlled conditions that prevent the patient from knowing, by sight, taste, texture, smell or any other means, what food is being given. The possibility of error in the diagnosis of gastrointestinal allergy is underscored by our experience with patients who are "clinically" sensitive to common foods but who failed to manifest any gastrointestinal symptoms whatever upon ingesting the suspected substances.²⁰ A twenty-year-old girl for example, stated that she could not eat fish because it caused vomiting and asthma, even getting near a fish market caused

would confuse rather than clarify the subject. In many reports, the material presented is insufficient, either to confirm or to discount whatever causative role is assigned to allergy. It appears preferable, therefore, to emphasize the methods used to demonstrate and diagnose allergic reactions of the gastrointestinal tract rather than to list opinions that are frequently conflicting. The measures used to demonstrate gastrointestinal allergy fall into three major categories: experimental studies, clinical observation and laboratory tests.

EXPERIMENTAL STUDIES

Experimental procedures do not provide conclusive evidence for the spontaneous occurrence of allergic reactions in the human gastrointestinal tract, but they do indicate that the gut, animal or human, may be the site of an allergic reaction causing recognizable local changes or disorders of function.

In sensitized dogs and rabbits, gastric ulcers were produced by Shapiro and Ivy⁸ after the injection of the antigen into the gastric mucosa. Ulcers in the stomach and duodenum were likewise caused in dogs by Friesen et al.¹⁰ using a special technique. An antiserum prepared against five antigens was injected into the gastric or duodenal wall or into the left gastric artery to induce local passive sensitization to the five antigens. Each of these was then injected into the systemic circulation on successive days to produce repeated allergic reactions in the sensitized area. Local edema without cellular reaction or eosinophilic infiltration was readily produced and was most marked two to six hours after injection of an antigen. Ulcers developed in some animals but were more frequent when the injections of antigen were associated with the administration of histamine in beeswax.

Although highly artificial, these experiments show that marked allergic reactions similar to those occurring elsewhere, notably the skin, may be produced in the gastrointestinal tract of animals. The circumstances in these experiments differ from those obtaining clinically in that injection was used for both sensitization and to elicit the allergic response. Experiments in guinea pigs have shown that systemic anaphylactic sensitization and the appearance of circulating antibody may follow ingestion of certain foods, such as milk¹¹ and egg white.¹² Sensitization arises, presumably, because the ingested antigen is absorbed into the circulation. In studies with egg white¹² prolonged feeding finally led to apparent failure of the antigen to traverse the gastrointestinal barrier. The antibody titer, having risen during the early feedings, fell during continued feeding, but quickly rose again when egg white was given by injection. The parallel between these observations and the well known tendency of children to outgrow clinically recognizable food

allergies is obvious. Leaving the more remote implications of these studies aside, there is clear evidence that the experimental animal may develop antibody and systemic anaphylactic sensitivity to antigens taken by mouth. However, these observations do not bear directly on gastrointestinal allergy because changes in the gastrointestinal tract itself were not seen. Furthermore, the circumstances of the experiments were again artificial because the antigens fed the animals were not normal constituents of the diet.

A closer experimental approach to the clinical aspects of gastrointestinal allergy is to be found in the work of Walzer and his co-workers.¹³⁻¹⁴ They injected serum obtained from a subject highly sensitive to peanut into the skin of the arm and into the mucosa of the rectum¹³ and the intestine in patients with ileostomy and colostomy.¹⁴ Introduction of peanut into the lumen of the bowel gave rise to edema at the sensitized sites in the skin and intestine at nearly the same time. Reactions in both sites also occurred when the peanut antigen was applied only to the sensitized site in the rectum or intestine. They considered that absorbed allergen reaching the sensitized site by way of the blood stream was primarily responsible for the reaction.

It was noted that, on rectal administration of the antigen, the edema at the sensitized (rectal) site began to develop slowly. This reaction preceded the lighting up of the control site on the skin by as much as six minutes. With the appearance and development of the cutaneous reactions the edema and erythema at the rectal site became more intense and rapidly reached its height.

They concluded that the local reaction "may be induced by antigen which is in direct contact with it or by absorbed antigen which reaches it via the circulation or by both."¹⁵

To these observations may be added the rare cases of abdominal pain, cramps, or diarrhea following overdosage during treatment of asthma or hay fever with injections of allergenic extracts. Especially significant is the much more frequent occurrence of nausea, vomiting, cramps, and diarrhea in persons being treated with pollen extracts by mouth.¹⁶⁻¹⁷ In these cases gastrointestinal symptoms were closely correlated with the administration of the allergen. Although the allergic nature of these symptoms need hardly be doubted, control studies were not done to rule out nonspecific irritation of the bowel.

These observations lead to the conclusion that under suitable circumstances marked allergic reactions may occur in the gastrointestinal tract, that systemic sensitization may be produced by ingestion of an allergen, and finally that the gastrointestinal mucosa may be sensitized with skin-sensitizing antibody (allergic reagin) and will react with edema on contact with the allergen, especially if this reaches the site by way of the blood stream.

doubted allergic background Bockus⁴³ believes that "Anxiety and tensional states, psychoneuroses, neurosis, vegetative and endocrinal disturbances, dietary and hygienic faults, and organic diseases account for abdominal symptoms in allergic persons much more commonly than do allergic reactions per se" Hence, a personal or family history of symptoms suggesting allergy does not appear to be a very reliable criterion when the role of allergy in either functional or organic gastrointestinal disorders is considered.^{4 5 44}

At times, gastrointestinal disorders are part of a syndrome originally described by Willan⁴⁵ ("purpura associated with violent vomiting, excruciating pain in the bowels, and anasarca swelling of the legs, thighs, and hands") but now often referred to as the Schönlein-Henoch syndrome. Attacks of this type were described in 29 patients by Osler⁴⁶⁻⁵⁰ visceral symptoms were usually associated with erythema, urticaria, angioedema, or purpura, but an occasional attack consisted of purely gastrointestinal disorders. Of the many patients with Schönlein-Henoch syndrome that have been reported since Osler's description, a few have been subjected to operation because of symptoms suggesting an acute condition of the abdomen. Abdominal pain in these cases must have been striking, but the operative findings have been inconstant. At times, the intestine has been edematous,⁴⁸ more often hemorrhagic,⁵¹ but frequently its appearance has been normal.⁵² Because some of the features of the Schönlein-Henoch syndrome resemble serum sickness, Osler⁵⁰ wrote, in typical style, "Before long the anaphylactic key will unlock the mystery of these cases." This suggestion has been readily accepted as an established fact, and Osler's cases are frequently cited as examples of gastrointestinal allergy.

Although Osler⁴⁶ stated that "the attack bears no relation whatever to food," several subsequent reports have ascribed this syndrome to food allergy.^{19 53-59} In some of these cases specific allergies may actually have been responsible for the Schönlein-Henoch syndrome. However, in most cases the relation of the symptoms to the alleged food allergen is not clear-cut. The interval between ingestion of the food and onset of symptoms ranges when given from fifteen minutes to nine days, in many cases the follow-up period appears inadequate, and in not a single case was the food given in a manner such that the patient was unaware of its nature.

Davis,⁶⁰ in reporting 44 cases of Schönlein-Henoch syndrome, did not consider food, drugs or other known allergens as the cause but emphasized that the attack frequently followed a hemolytic streptococcus infection. Similar observations were made by Gairdner,⁶¹ who, on the basis of his own cases and a review of the literature, suggested that the syndrome is linked clinically, pathologically and

etiologically with acute nephritis, rheumatic fever and polyarteritis nodosa. The syndrome of purpura, urticaria and gastrointestinal symptoms, it is apparent, may be a manifestation of hypersensitivity, but evidence that it is caused by ingestion of allergenic foods is inconclusive.

In a number of cases suffering from abdominal pains believed to be allergic in origin, an injection of epinephrine has been followed by relief within thirty minutes. This effect has been held to substantiate the allergic nature of the complaint.^{52 62} That epinephrine might alleviate gastrointestinal allergy as it relieves asthma and urticaria is a reasonable hypothesis. On the other hand, a sympathomimetic agent like epinephrine may be transiently spasmolytic as well. Relief of nonallergic symptoms by epinephrine is a possibility that detracts from its use as a therapeutic test in the diagnosis of abdominal allergy.

In summary, the diagnosis of gastrointestinal allergy by clinical means depends principally upon the patient's incrimination of specific foods, the effect of trial diets and association of the gastrointestinal complaints with manifestations usually believed to be allergic. Analysis of these criteria reveals them as quite unsatisfactory. The reliability of trial diets, theoretically the best of these diagnostic measures, is impaired by the expectations and the attitudes of the patient and by difficulties in execution and interpretation, but most of all by the vague nature of gastrointestinal allergy itself. A clear-cut, if tentative, definition of what constitutes gastrointestinal allergy must be made before the clinical diagnosis of this condition can achieve precision.

(To be concluded)

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these symptoms. Skin reactions to fish were strongly positive. However, a freshly prepared fish extract, also causing a marked skin reaction of the immediate type, was introduced into the stomach by stomach tube in a manner to prevent the patient from knowing that fish was being introduced. No symptoms occurred, and there was no change in the stomach or small intestine recognizable by fluoroscopy. Furthermore, no delayed symptoms occurred.

If gastrointestinal allergy were a well defined entity with respect to etiology, chronologic sequence, reaction and reproducibility, the information obtained from the patient's history and test diets would be far more conclusive. If, for example, the ingestion of a certain amount of a specific food always produced the same symptoms within a certain interval, psychogenic and allergenic disorders could be differentiated quite satisfactorily. Unfortunately, as the following paragraphs indicate, the characteristics claimed for gastrointestinal allergy are extremely variable.

Alvarez and Hinchshaw¹⁵ state that an offending food may be recognized because symptoms regularly follow its ingestion within a period of one to twelve hours, and usually within three hours. Others, however, do not subscribe to this viewpoint and maintain that sensitivity to foodstuffs may be variable, intermittent, cumulative, nonquantitative and characterized by unpredictable time relations.^{2, 23, 29, 31} Some believe that a patient's sensitivity may vary because of climate, season, dietary habits, intercurrent infection, endocrine activity, emotional states or spontaneous immunologic fluctuations.^{6, 22, 32, 33} It has also been suggested that food may contain seasonal contaminants³³ (pollen in milk, for example), thereby explaining an inconsistent relation between symptoms and ingestion of the suspected agent. According to Vaughan,³⁴ a food may be eaten with impunity for days until a cumulative effect brings about symptoms. Others^{26, 35} believe just the opposite: if an allergenic food is eaten often enough, the allergy may be "masked," and a clear reaction may only be seen if ingestion of the food is preceded by a period of elimination. The interval between eating of a suspected food and ensuing symptoms may also be affected by the site of the sensitized gastrointestinal tissues and by the effects of digestion. The stomach, for example, might react within a few minutes of eating, but, unless the allergen is bloodborne, the colon might not be affected for forty-eight hours. The effects of digestion are disputed. Olmsted et al.³⁶ recommend as nonallergic a diet consisting principally of protein digests (amino acids and polypeptides), glucose, and vitamins. On the other hand, the products of protein digestion³⁶⁻³⁹ and even glucose²⁶ have been suggested as possible allergenic agents. If polypeptides, "proteoses,"⁴⁰ and "propeptans"⁴¹ are responsible for gastrointestinal allergic manifestations, the onset

of symptoms will obviously depend on the rate of digestion.

From a practical viewpoint, elimination diets are difficult to apply. Since allergy to minute quantities of food is believed possible,^{2, 26} the patient must exercise great care to avoid even the smallest quantity of any food, condiment or drink that is prohibited. Some patients are either too ignorant or too careless to follow such meticulous regimens. Others, dependent upon the processed foods so extensively used today, violate rules innocently. Even the cornstarch paste used in sealing cardboard food containers may, according to Randolph,⁴² contaminate the contents sufficiently to cause symptoms of gastrointestinal allergy. Whatever the reason, the success of an elimination diet is frequently threatened by its practical difficulties, particularly if a patient is believed to be sensitive to several foods.

Interpretation of many of the reported cases in which trial diets were applied to the diagnosis of gastrointestinal allergy is difficult because particulars are omitted. Although it is often stated that symptoms disappear after removal of a food, the duration of the symptom-free period may not be given. If symptoms persist during allergic management, their recurrence is usually attributed to unwitting ingestion of the incriminated food, evidence for which is sought by the most detailed and laborious history taking. That this may lead to serious error can be readily appreciated when it is realized that equally detailed histories may not be taken when the patient is well. Thus, repeated exposure to the allergen without development of symptoms is not excluded. On the other hand, when the patient eats the incriminated food with impunity, the discrepancy is often explained away by a number of assumptions, such as the existence of masked allergy, desensitization by repeated exposure, and refractory periods.

The tendency of more than one allergic manifestation to occur in patients with rhinitis, asthma, eczema and hives has led to the view that gastrointestinal symptoms occurring in such cases are often allergic in origin. However, the allergic nature of the reactions in the skin or respiratory tract is not always established beyond a reasonable doubt. In many cases of asthma, eczema and hives, demonstration of a causative allergen is difficult, and such manifestations are sometimes considered allergic chiefly because their clinical characteristics are similar to those in which the operation of an antigen-antibody reaction may be considered settled. Thus, a personal or family history of asthma, urticaria or eczema in a patient with gastrointestinal symptoms or abnormalities merely suggests an allergic tendency but in no way establishes the diagnosis of gastrointestinal allergy. Furthermore, gastrointestinal symptoms are so common that they may arise from a variety of causes even in patients with an un-

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CASE 35341

PRESENTATION OF CASE

A twenty-two-year-old unemployed laborer entered the hospital because of visual difficulties.

The patient grew normally until the age of about thirteen years, when he realized that he was not as tall as other children. After fifteen years he stopped growing in height altogether. At the time of entry he measured 5 feet, 3 inches. His hat size was 7½ and his shoe size No. 8. He never developed axillary hair. He occasionally had erections and nocturnal emissions. Seven years before entry he first noticed that he had a squint, the left eye turning out. At the same time he began to have severe headaches which were usually "behind the eyes" and lasted from several hours to a day. They had become less frequent during the past year or two. Three years before entry the patient began to complain of inability to see well to either side. Because of this he bumped into things, particularly on the left. The patient did well in school and finished the second year of high school, after which he had to go to work. He supported himself as a laborer. His only complaint aside from his eyes was a chronically poor appetite.

Physical examination showed a patient who appeared more like an adolescent boy than a man of twenty-two years except for a peculiarly old facies with wrinkles about the eyes and mouth. His head was disproportionately large, and the extremities seemed too long for the body. The neck was short. Except for scanty growth of pubic hair, the skin was smooth and hairless. The skin of the distal phalanges was hard and shiny. The heart, lungs and abdomen were normal. The testes, penis and prostate were small. The left dorsalis pedis artery was not palpable. Both eyes were rather prominent. Vision was 20/20 on the right and 20/200 on the left. The left optic disk was pale, the right was normal. The left eye diverged about 25°, and the cranial nerves

were otherwise normal. The musculature was somewhat underdeveloped, but there was good strength. Sensation was normal.

The temperature, pulse and respirations were normal. The blood pressure was 90 systolic, 70 diastolic.

The fasting blood sugar was 67 mg per 100 cc. After 4.5 units of regular insulin, it was 26 mg per 100 cc in thirty minutes and 36 mg in one hour. At that point 0.4 cc of 1:1000 epinephrine was given intravenously. This was immediately followed by extreme anxiety, rapid pulse and pallor and a drop in blood pressure lasting about two minutes. The blood sugar curve was not affected and gradually returned to a level of 64 mg per 100 cc after a total of three hours.

The serum cholesterol was 320 mg and the cholesterol esters 241 mg per 100 cc.

The 17-ketosteroids in a twenty-four-hour urine sample were 0.4 mg.

The spinal fluid was normal with a pressure equivalent to 150 mm of water and a total protein of 26 mg per 100 cc. The basal metabolic rate was -22 per cent.

X-ray examination of the pelvis showed the epiphyses of the femoral heads to be closed. Those of the ilia were just closing. The epiphyses of the elbows, wrists and knees were closed but not fused. There was enlargement and destruction of the sella turcica. The posterior clinoids could not be traced but in their stead there was an area of calcification extending upward for half an inch. A pneumoencephalogram showed the bodies of the lateral ventricles to be elevated and obliterated along the lower margin. The third ventricle appeared to be displaced backward. The aqueduct was somewhat erect. There was no dilatation of the lateral ventricles. The intelligence quotient was 107, and psychometric tests did not reveal any definite indications of brain disease.

On the fifteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. BERTRAM SELVERSTONE: Like so many patients who do not mature normally because of anterior hypopituitarism, this young man had apparently come to accept himself as he was—different from others but not alarmingly so. He complained chiefly of visual difficulties, a "neighborhood symptom." The stigmas of failure of the anterior pituitary body are, however, clear. A deficiency of growth hormone had apparently been present since before the age of thirteen, at which time he first noted his shortness of stature. Sparse pubic hair, absent axillary hair and small genitalia point to early hypogonadotropic eunuchoidism. The disproportionate limb length suggests an associated delayed closure of epiphyses and the roentgenograms of the long bones confirm this impression. Deficiency of thyroid

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DIFFERENTIAL DIAGNOSIS

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stimulation by thyrotropic hormone will explain the low basal metabolic rate and elevated serum cholesterol. There is evidence also of deficiency of the adrenocorticotrophic hormone, the low arterial pressure and increased sensitivity of the blood glucose concentration to the administration of a small dose of insulin are important in this connection. Presumably, a severe impairment of glycogen storage in the liver was present, as shown by the failure of the lowered blood glucose to rise when a large dose of epinephrine was administered. We may consider this anomaly of carbohydrate metabolism to be a manifestation of deficiency in glucocorticoids, resulting also from lack of adrenocorticotrophic hormone. The extremely low value for urinary 17-ketosteroids reflects the deficiency both in gonadotropic and in adrenocorticotrophic factors. I should not consider abnormal the extreme cardiovascular and emotional response that resulted from the intravenous administration of 0.4 cc of 1:1000 epinephrine. This was an unusually large intravenous dose and could well have produced these alarming symptoms in a normal person. The curious admixture of youth and senility in his appearance is a common feature of hypopituitarism. Perhaps Dr. Albright can tell us the precise endocrine basis of this phenomenon.

The manifestations that with respect to the pituitary body, we call "neighborhood symptoms" were apparently more important to the patient. It is not surprising that squint and headache were complained of for four years before he noted visual impairment, since an acuity of 20/20 was still present in the right eye at the time of admission. The headache is significant—it was not the bitemporal aching pain often present when the diaphragma sellae is stretched by an intrasellar tumor but was a pain "behind the eyes." This is suggestive of pressure on the tentorium, although pain may be referred to this region from other portions of the basal dura. The left external strabismus is suggestive of pressure on the oculomotor nerve although other manifestations of such pressure were not noted. Pressure from above, as by a herniated hippocampal gyrus, usually produces pupillary dilatation as a first sign of compression of this nerve against the free edge of the tentorium. The arrangement of fasciculi in the nerve is such that pressure from an anterior direction might well produce an early extraocular muscle weakness. Pressure on the third nerve at its entrance into the cavernous sinus, or even within the sinus, might also produce this picture. The patient complained for three years of inability to see well to either side, and apparently his symptoms were worse on the left side. The pale left optic disk, with 20/200 vision on the left, confirms the impression that this patient may have had originally a bitemporal hemianopsia, which later spread to include the macular field on the left. Unfortunately, objective determination of the visual fields is not mentioned in the case summary. All that we may say, however, that there was

evidence of chiasmal compression, more marked on the left side. That the lesion was only slowly progressive is suggested by the normal psychometric examination and normal cerebrospinal fluid pressure.

We have, then, a young man who presents evidence of a lesion of at least nine years' duration, involving the basal dura, optic chiasm and possibly the left oculomotor nerve. The anterior pituitary had been progressively compromised, without evidence of impairment of posterior pituitary function.

A number of lesions in the region of the sella turcica can produce a clinical picture with some of the features presented by this patient. Although two or three earlier cases appear in the literature, chromophobe pituitary adenomas are usually not manifest until after the age of fifteen years. They do not produce the suprasellar calcification mentioned in the description of the roentgenograms. Glioma of the optic chiasm could be considered also, but preservation of even 20/200 vision in the left eye and normal visual acuity in the right after so long a period would be most unusual. Then, too, a severe endocrine disturbance is most uncommon with such lesions. Meningioma of the tuberculum sellae may occur at twenty-two but would be most unusual at thirteen years, when symptoms were first noticed. Endocrine abnormalities are usually not a feature of this tumor and an elevation of cerebrospinal-fluid protein would probably have been noted. Arachnoiditis of the optic chiasm could produce visual changes such as those described, but pituitary dysfunction is not a feature of the disease and calcification, if it occurs, is in a position anterior to that described. Curiously enough, occasionally in obstructive hydrocephalus, the floor of the third ventricle may be ballooned downward sufficiently to produce chiasmal compression and pituitary hypofunction. The normal cerebrospinal-fluid pressure and the pneumoencephalographic findings effectively rule out such a disorder.

A variety of hamartomas may occur in the midline at the base of the brain. Cushing* reported, in 1912, a case of Osler's in which a teratoma the size of a golf ball was found in the interpeduncular fossa of a sixteen-year-old seamstress. Dermoids and lipomas may also be seen. The cholesterol deposits of Hand-Schüller-Christian's disease characteristically affect the neurohypophysis rather than the anterior lobe. Chordoma of the basisphenoid should also be mentioned. Chordomas usually run a briefer course, but one such lesion of eighteen years' duration has been reported. Much more extensive destruction of the base of the skull would probably have occurred during the nine years of this patient's story, and a nasopharyngeal mass would have been likely as well.

If we proceed now to a more detailed consideration of the roentgenographic findings, we are led to

*Cushing, H. *The Pituitary Body and Its Disorders*. 341 pp. Philadelphia: J. B. Lippincott Company, 1912. P. 43.

a more common clinical entity. The description of enlargement of the sella turcica with an area of calcification extending upward from the region of the absent posterior clinoids is that of the cystic or solid tumor of a Rathke-pouch remnant variously called craniopharyngioma or adamantinoma. Such calcification is seen in 70 to 85 per cent of these lesions. The term "destruction" is used also in describing the sella. If true destruction, as opposed to erosion by pressure, was present, we must consider also the carcinoma, which occasionally arises in such a lesion. The description of the pneumoencephalogram is consistent also with craniopharyngioma, an unusually large one, extending under the frontal lobes and probably adherent to mammillary bodies, midbrain and pons as well. I cannot be certain whether the lesion was primarily cystic ("suprasellar cyst") or solid. The former would offer a much more favorable prognosis.

CLINICAL DIAGNOSIS

Craniopharyngioma

DR SELVERSTONE'S DIAGNOSIS

Craniopharyngioma (adamantinoma) with secondary hypopituitarism

ANATOMICAL DIAGNOSIS

Suprasellar epidermal cyst

PATHOLOGICAL DISCUSSION

DR CHARLES S KUBIK. Operation by Dr William H Sweet disclosed a cystic suprasellar tumor with a dense, fibrous capsule and contents consisting of yellowish, avascular, soft solid, flaky material, which was removed by spoon and suction, leaving an "enormous" cystic cavity. The material appeared to be typical of epidermoid cyst, not only on gross inspection but also microscopically, consisting of faintly outlined epithelial cells and containing cholesterol crystals. The cyst wall, of which only a small piece was removed, was composed of dense connective tissue. Although no epithelial lining was included with the biopsy specimen, the character of the flaky material removed left little or no doubt that this was a cyst lined with epidermal cells, sometimes also known as "cholesteatoma" and "pearly tumor." The flaky material consists of accumulated desquamated epithelial cells.

Epidermoid cyst of the region of the chiasm is considerably less common than craniopharyngioma, but we have had 2 or more other cases. In at least 1 of them there was a homonymous hemianopsia, and the tumor was on one side, as in this case. They may occur in other parts of the cranium and cranial cavity—for example in the orbit, cerebellum, inter-cerebral fissure, temporal bone and other parts of the skull.

In this case the patient made a good recovery. His headache was relieved. The visual acuity of the left eye did not improve, and the homonymous hemianopsia persisted.

CASE 35342

PRESENTATION OF CASE

A seventy-year-old Irish housewife entered the hospital because of extreme weakness.

Five weeks prior to admission she noted the onset of excessive weakness and "tiredness." Shortly thereafter she began to suffer continuous dull, aching, nonradiating, epigastric pain unrelated to meals. This was associated with mild nausea and occasional vomiting without hematemesis. Vomitus either was watery and sour or contained undigested food, depending on time relation to previous meal. There was mild loss of appetite. No irregularity of bowel habit was noted and the stools were free of blood. Two weeks prior to admission the urine became "red," and the stools light in color. A physician made a diagnosis of "yellow jaundice" for which "white pills" were prescribed. Weakness was progressive and finally required hospital entry after "her knees suddenly gave way" as she was walking about her house. Consciousness was not lost during this episode, nor were there any other symptoms referable to the central nervous system. There had been a 20-pound weight loss during the preceding three months. Moderate generalized pruritus was a troublesome symptom from the onset of the present illness.

Twelve years before entry she developed an indolent ulcer on the second toe of the left foot. She was found to be mildly diabetic but was rapidly standardized with a daily dose of protamine zinc insulin of 36 units daily. The toe was amputated, and the pathological report was acute and chronic osteomyelitis. From that time on she attended the Out Patient Department sporadically. The diabetes remained under good control without significant alteration in insulin requirement.

Physical examination disclosed an extremely obese, deeply icteric woman able to lie comfortably, flat in bed. The body weight was 215 pounds. Numerous cutaneous excoriations were prominent, but there was no superficial lymphadenopathy. The heart and lungs were clear. Minimal tenderness without muscle guarding was elicited in the right upper quadrant of the abdomen. The liver edge was palpable 15 cm below the right midanterior costal margin "with the suggestion of another edge 5 cm above the liver border." Owing to the patient's obesity it was impossible to determine the character of the liver or to establish the presence or absence of nodules. There was a minimal rectocele, but no masses could be palpated on digital examination. There was no edema of the extremities,

and pulsations were palpable over the dorsalis pedis and popliteal arteries. The Achilles and patellar reflexes were not elicited, but the biceps reflexes were active and equal.

The blood pressure was 130 systolic, 58 diastolic. The temperature, pulse and respirations were normal.

The urine was acid and the specific gravity ranged from 1.008 to 1.016. There was a + to +++ test for albumin. The urine contained sugar (green) on only one occasion. Many granular casts and leukocytes were noted in the sediment. Bile tests were ++++ at all times, but the urinary urobilinogen was negative. Examination of the blood showed a red-cell count of 3,900,000, with a hemoglobin of 12 gm., and the white-cell count ranged from 15,000 to 22,000 with neutrophils ranging from 84 to 92 per cent. The stools were pale and guaiac positive on two occasions. The blood sugar was 237 mg. and the nonprotein nitrogen 66 mg. per 100 cc. The cephalin-flocculation test was + in 24 hours and ++ in forty-eight hours, the lipase was 2.5 cc. The total protein was 5.51 gm. per 100 cc., with 2.83 gm. of albumin and 2.68 gm. per 100 cc. of globulin. The van den Bergh reaction was 20 mg. per 100 cc. direct and 24 mg. per 100 cc. indirect. The prothrombin time was 16 seconds (control 15 seconds). The carbon dioxide was 21.6 milliequiv. per liter, the phosphorus was 4.9 mg. per 100 cc., and the alkaline phosphatase 43.0 units per 100 cc.

Adequate fluoroscopic study of the gastrointestinal tract was impossible because of the patient's size and debility. On routine films the right leaf of the diaphragm was higher than usual but the lung fields were clear. The esophagus contained a tube but was otherwise not remarkable. No localized disease was detected in the stomach. There was a suggestion of a filling defect measuring approximately 2.5 cm. on the medial aspect of the second portion of the duodenum. The duodenal loop, however, did not appear enlarged. The liver shadow appeared enlarged.

Following admission the patient had no complaints other than weakness. She tolerated a soft diet well for twenty-four hours but then began to vomit all food eaten. For this reason food was withheld, and parenteral feedings were employed. A gastric tube was passed and left in position in order to aspirate barium following the gastrointestinal series.

On the fourth hospital day she became disoriented. On the following day she became stuporous, but the diabetes was considered under fair control. Her course was one of rapid deterioration. Coma supervened on the following day, and death occurred twenty-four hours later. During the last day of life the temperature rose to 101°F, the pulse to 100, and the respirations to 25.

DIFFERENTIAL DIAGNOSIS

DR DANIEL S. ELLIS: As I read this case over, it seemed to me fairly easy to make a diagnosis that would explain most of the reported findings.

Let us, for the moment, consider this patient's diabetes. This was of twelve years' duration. Apparently it was mild, of the type seen in elderly people, and was easily controlled although she had one gangrenous toe, which was amputated. She could possibly have gone into diabetic coma during the last few days of her life. But had she done so, I am sure that we would have had laboratory and clinical evidence of it. Next let us consider infection. I cannot find any real evidence of a chronic suppurative process. It is true that she had a high white-cell count, with a high neutrophil count. She was afebrile until the end. There is nothing else in the record to suggest any chronic suppurative process unless, perhaps, one is going to say that she had chronic pyelonephritis.

I am left with the problem of deciding whether or not this patient had obstructive jaundice due to mechanical block in the extrahepatic biliary tree or diffuse parenchymal disease of the liver. I believe very strongly that her death was due to disease in her liver, yet there is little evidence to make a diagnosis of diffuse parenchymal disease in the nature of hepatitis, cirrhosis or yellow atrophy. The cephalin-flocculation test, which I would expect to have been +++ or ++++ if the jaundice and liver disease had been caused by hepatitis or cirrhosis, was normal. The fact that she had no urobilinogen in the urine, although she had plenty of bile present, is strongly in favor of an obstructive type of jaundice. In addition, the patient had itching of three months' duration. If that were on the basis of parenchymal liver disease, hepatitis, cirrhosis or biliary cirrhosis, almost surely there would have been other laboratory evidence of such a condition. One frequently sees itching as a presenting symptom in obstructive jaundice, or of disease involving the liver or extrahepatic biliary tree, long before jaundice supervenes. So we have several findings very strongly in favor of an obstructive process: the long history and itching, the high alkaline phosphatase, the light-colored stools, and the lack of urobilinogen in the urine.

The x-ray report mentions something in the second portion of the duodenum. This is, of course, one of the places that we want to look at, and a gastrointestinal series should be done on all patients with unexplained jaundice, even though they have not had nausea or vomiting or anything else to point to gastrointestinal disease.

Dr. Wyman, will you show the x-ray films? I would like to be sure that this woman had some significant finding in the second portion of the duodenum.

DR STANLEY M WYMAN The right leaf of the diaphragm is considerably elevated, and the liver appears considerably enlarged. The lung fields are not remarkable grossly. A gastrointestinal examination was done in the supine position only. I could not examine the esophagus because of the presence of a large tube, which one can see in the lower esophagus. The stomach itself was very large and contained retained fluid, but there was no evidence of gross intrinsic disease of the stomach. The duodenal loop was impossible to see well fluoroscopically, but there appeared to be a pressure defect of the second portion of the duodenum on its medial aspect, measuring perhaps 2.5 cm in diameter. This is seen on one film well, is only suggested on this second film and is inadequately seen on this third film.

DR ELLIS Anatomically, is that where the ampulla of Vater is or where the common duct lies going through the duodenal wall?

DR WYMAN I think this area is in or about the ampulla of Vater. I thought she had a tumor of the ampulla, or distal common duct, or else a non-opaque stone. Examination, of course, was not ideal.

DR ELLIS To tie in with Dr Wyman's findings, this woman had a positive guaiac reaction on the stools. The nausea and vomiting were not necessarily due to any lesion in the stomach or gastrointestinal tract. They may have been caused by the severe disease that I am assuming she had in the liver or in the biliary tract somewhere. There is nothing to suggest an increase in the width of the duodenal loop due to a carcinoma of the pancreas.

As Dr Wyman has told you, we have no evidence of intrinsic disease in the stomach itself.

I cannot make any case for an extremely fatty liver, other than the fact that she was obese. We are not told of any alcoholic history. One of the things that can cause this picture of deep jaundice, a sudden and progressive onset to fatal outcome, is an acute fatty alcoholic liver in which no normal cells, or practically none, are observed in histologic sections. The liver may be large, and the skin deep orange. The history may not suggest it at all. The laboratory tests at that time may be so equivocal and the process so relatively acute that they have not had a chance to reach the point where they would show evidence of parenchymal disease. This is just a possibility that I must think about and that must be ruled out. It would be of help to have had an aspiration biopsy from the liver. It might have revealed whether or not she had diffuse fatty infiltration of the liver or metastatic disease in the liver.

This patient may have had a pylephlebitis due to some focus of infection of which I am not aware. I will do no more than mention that as a possibility. I cannot rule out the presence of lymphomatous disease.

I really believe that this woman had metastatic carcinoma involving the liver. That is the one condition, or one of the conditions, that will give a tremendous liver and a high alkaline phosphatase. The question is: Where did the carcinoma come from? It could have come from the stomach. There is one suggestion that there was a mass on top of the mass of liver. It is pointed out in the protocol that the mass was felt 5 cm above the margin of the liver. One wonders if the mass was gall bladder and the upper mass was the liver edge. The x-ray studies do not indicate carcinoma of the stomach. Therefore, I cannot hold to that diagnosis.

Carcinoma of the head of the pancreas frequently metastasizes to the liver. It may metastasize to the porta hepatis, without metastasizing elsewhere, and cause obstructive jaundice. If this was such a case, I cannot explain the tremendous size of the liver reported.

Could this patient have had gallstone? She certainly could. If so, it was a silent stone and apparently in the common duct if the jaundice was due to it.

We are now left having to explain her death and her large liver. I would not think she had been sick long enough, or had jaundice long enough, to cause her death if all this was on the basis of simple obstruction. For that reason, I believe that this woman had a carcinoma of the biliary tract, probably in the common duct or ampulla of Vater, and that she had metastases all through the liver, producing hepatomegaly and leading to hepatic failure. Metastases in the liver frequently do not manifest themselves until the patient is almost in a terminal stage. I think that her sudden death was due to extensive involvement of the liver by cancer. The blood in the stools was probably on the basis of an ulcerative tumor of the common duct or the ampulla of Vater. In a certain number of cases, however, deeply jaundiced patients may have guaiac-positive stools without any ulcerative lesion.

The protocol reports albumin and granular casts and some cellular elements in the urine. This in a woman seventy years might simply be a finding that one frequently sees in an arteriosclerotic person who is extremely ill. I suppose, because of the large number of cellular elements, I have to say that there was some factor of pyelonephritis here, but I find it hard to say that that was any more than a concomitant finding and it did not play a part in the terminal episode.

Carcinoma of the biliary tract, probably arising in the common duct or ampulla, with metastases to the liver, was my first impression to explain this case. I still stick to it and am fully prepared to find out that something existed that I have not mentioned. The x-ray report of a deformity in the region of the ampulla leads me to exclude primary hepatoma as a possibility.

CLINICAL DIAGNOSIS

Carcinoma of ampulla of Vater

DR ELLIS'S DIAGNOSES

Carcinoma, biliary tract
 Extensive and diffuse metastases to liver
 Diabetes mellitus
 Generalized arteriosclerosis
 Arteriosclerotic kidneys — ? pyelonephritis

ANATOMICAL DIAGNOSES

Carcinoma of gall bladder
Thrombosis of hepatic and portal veins, neoplastic
Massive infarction of liver
 Intercapillary glomerulosclerosis
 Cholelithiasis
 Neurofibroma of esophagus
 Carcinoma of right breast

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Autopsy showed a liver filled with carcinoma as Dr Ellis had suspected. It took a little longer to clear up the question of the primary site. There was no tumor at the ampulla of Vater. There was a shallow benign peptic ulcer in the duodenum, which was probably responsible for the blood in the stools. The gall bladder was greatly enlarged and was obviously the edge that was clinically interpreted as liver, whereas the second "edge," 5 cm higher, was the true liver margin. There was a large stone impacted in the ampulla of the gall bladder, and the walls of the gall bladder showed papillary excrescences and one rather large necrotic mass that could have been inspissated secretion or totally necrotic tumor. There was no doubt that the carcinoma arose in the gall bladder.

One of the surprises of the autopsy was that the veins throughout the liver, both portal and hepatic, were extensively thrombosed. There was mas-

sive secondary infarction of liver substance. The thrombus from the hepatic vein had extended up into the inferior vena cava in a form that could be called Chiari's disease. These thrombi consisted in large part of fibrin and platelets but also had many tumor elements in them. Hepatomas, of course, commonly invade the hepatic vein. It is rare for a tumor arising in the gall bladder, as we are sure this one did, to do so, but it is not impossible.

We found a number of coincidental lesions. There was a small intraductal carcinoma of the right breast, which had not produced metastases. The esophagus contained a submucous neurofibroma of significant size, 1.5 by 3 cm, which had apparently produced no symptoms, and there was a colloid adenoma of the thyroid gland.

The patient was enormously obese and deeply jaundiced, and post-mortem examination was delayed for fourteen hours so that post-mortem decomposition was severe and microscopical sections are not of very much help. We did, however, think that we could recognize enough in the kidney to say that she had the Kimmelstiel-Wilson type of glomerular change that is so commonly seen in advanced diabetes. There was slight pyelonephritis. I do not believe either lesion was responsible for any significant symptoms and death was explained first by carcinoma and secondly by acute liver insufficiency and liver necrosis, dependent on a massive thrombosis of the veins throughout the liver substance.

DR ELLIS I think it is amazing how far cancer of the liver, especially metastatic, can go before it is recognized. I did not bring out the fact, as Dr Mallory has done, that the terminal episode is frequently due to some such processes as occurred here.

DR BENJAMIN CASTLEMAN How large was the liver?

DR MALLORY It weighed 3500 gm.

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IMPROVED BLUE SHIELD BENEFITS

THE Blue Shield program in Massachusetts has undergone recent changes some of which will widen its scope and all of which should increase its value.

A surgical-obstetrical but nonmedical contract will be reissued to compete with the low-cost surgical-obstetrical contract now issued by commercial insurance companies. It is unfortunate that internists are at present excluded from participating in this part of the Blue Shield program, but in this instance price, and not benefits, is the determining factor.

Both the new surgical-obstetrical and the present medical-surgical-obstetrical contracts will be offered to nongroup subscribers who are not eligible for group enrollment. Two years ago contracts were offered to nongroup subscribers, but the difficulties toward which Blue Cross was at that time headed forced the suspension of nongroup enroll-

ment in both organizations. As of September 1, 1949 nongroup enrollments will be available to every healthy applicant in the Commonwealth.

A change in subscription rate will be rendered necessary by this new policy. The yearly subscription rate of \$29 per family has been found insufficient to cover the losses sustained on families in the nongroup and conversion categories. The conversion category consists of those subscribers who leave their place of employment, about half of whom allow their insurance to lapse. Many of the remainder retain their coverage because of the anticipation of medical care. Consequently the rate for these two categories only will go from \$29 to \$32 per year.

Certain clarifications have been made in the provisions of both surgical-obstetrical and medical-surgical-obstetrical contracts. Benefits will be provided for the care by a pediatrician of a premature baby weighing four and a half pounds or less. Benefits will not be provided for the circumcision of an infant during the first year of life, as such an operation is practically never a surgical necessity.

A member who uses private accommodations in a hospital when private accommodations are not medically necessary and ward accommodations are available, becomes thereby a limited or overincome member, subject to an additional charge by the attending physician. It is believed, however, that the profession should exercise extreme caution in availing itself of this provision.

A one-year waiting period will go into effect for nongroup members before benefits will be provided for care or treatment of any condition existing in any form on the effective date of the subscription agreement.

The best way to defeat compulsory health insurance is to render voluntary insurance more desirable. This the various medical-service plans of the country are successfully accomplishing.

"SING OUT SWEET LAND"

By action of the Council of the Massachusetts Medical Society taken at its annual meeting on May 25, the appointment of a co-ordinating committee to co-operate with the National Education

Campaign of the American Medical Association was confirmed. The committee, which has been functioning since April, is composed of the officers of the Society, the delegates to the American Medical Association, representatives from the committees on medical economics, legislation, public relations and the subcommittee on national legislation, the director of information and education, and the editor of the *Journal*. The chairman is Dr. Frank H. Lahey, former president of the American Medical Association.

The committee considers the time now appropriate to render an account of its activities as well as to offer its program for the future.

Of special importance has been the assembly that took place on May 1 at the Hotel Statler, to which each district society was invited to send ten per cent of its members. The attendance was estimated at six hundred and considerable enthusiasm for the campaign was evidenced.

A speaker's bureau has been established and some twenty physicians have given nearly three hundred talks before various lay groups. Editorial support has been elicited and numerous press and radio writers and commentators have supported the campaign to bring the Association's program before the public. Many lay groups have been active and a number of organizations have passed resolutions in support of the medical profession. Much literature has been distributed, and more is available at the Society headquarters.

Although the Government's campaign in favor of compulsory health insurance has been relatively inactive of late, the co-ordinating committee is planning its own future program. This is based largely on the activities of the district societies, most of which have not yet swung into satisfactory action, Franklin being a notable exception.

District co-ordinating committees must be set up where they are still lacking. Co-operation with the "Tell it to Twenty" division of the Massachusetts campaign must be strengthened, in order that a continuous flow of information to the list of twenty contacts made by each physician may make an informed group capable of substantial action and results at the proper time. Resolutions against compulsory national health insurance should

be adopted by every district society and auxiliary. Local press and radio committees should be organized and contact made with local professional groups. Lay speakers must be enlisted, and above all the district woman's auxiliaries must be utilized in the campaign.

If socialized medicine is to form the wedge for a socialized state, it shall not be for lack of an informed and intelligent opposition.

DONORA SMOG

OF THOSE few freedoms that remain to hunted man, the air he breathes has been considered as a fundamental right, common to all. Even the air, however, as the dweller in industrial areas well knows, may become as polluted by mechanical progress as are the water courses of the world's more advanced nations.

Uncontrolled (although largely controllable) smoke has been one of the by-products of the fiercely burning fires of industry, increasingly being shown to constitute a hazard to health as well as an offense to the eyes and a stench in the nostrils.

Especially spectacular were the conditions that prevailed for a short period last fall over Donora, Pennsylvania. Here, apparently as the result of static atmospheric conditions combined with the proximity of the American Steel and Wire Company zinc plant, a so-called "smog" descended over the city and presumably precipitated the deaths of twenty susceptible persons.

As a result of this episode the Public Health Service of the Federal Security Agency conducted a test in April to determine, if possible, the cause of the disaster. During the test the plant gradually resumed full production with no evidence of unfavorable conditions resulting. The assumption is that an unusual atmospheric state was necessary to trap in the valley of the Monongahela River the effluvium of the plant.

The knowledge is reassuring that lethal conditions will only occasionally result from the chance association of industrial production and bad weather. It is disturbing to realize that progress in public health must be made across the deserts and over the pol-

luted streams and through the poisoned air that man is himself creating

Perhaps out of the almost forgotten disaster at Donora will come something more tangible than the perpetuation of an accordion-pleated word

MOUSE TOWER

THE story, recently released, of Columbia's mouse dairy is another reminder of the unique relations that exist between mice and men. Rats and mice for better or for worse—but principally the latter—have exercised their influence over human affairs since rats and mice and men began

Hamelin had its experience with rats and learned too late that it pays to pay the piper. In the tenth century a singularly unworthy ecclesiastic, Bishop Hatto, having oppressed the peasantry of his fief and becoming annoyed at their protestations, shut them all into a barn, which he burned. Their squeals he likened to the squealing of mice.

As famine spread over the land a plague of rodents appeared to escape which Bishop Hatto fled to his well stocked tower on an island in the Rhine. The Rhine, as history has shown before and since proved no barrier to a determined invader. The mice crossed it, stormed the castle, and devoured the squealing bishop, presumably in some upper chamber.

Columbia's mouse tower in the College of Physicians and Surgeons, twelve years old and sixteen stories high, differs in its conception from that of Bishop Hatto.

At a cost of about \$10,000 a quart, two quarts have been obtained annually from several thousand mice each of which has been milked regularly (by suction), producing an average of 1 cc of milk per pregnancy.

The result of this costly dairy, however, the story of which is contained in a release from Columbia University has been a long forward step in the study of cancer. Certain strains of mice are peculiarly susceptible to a cancer of the breast that closely resembles the human form. The cancer virus has been isolated in the milk of these high-cancer-strain mice. This milk when introduced into the systems of other mice male or female, of low-cancer or high-

cancer strain, by ingestion or injection, gives rise to cancer in a high percentage of cases.

The destructive rodent has made another part payment on the debt it owes to humankind.

Dr Thomas Hooker was prosecuted in Canada, recently, on complaint of the College of Physicians and Surgeons, for practising physic without license, and fined £10 and costs. He had better come into New England where any body can practise medicine whether they understand it or not.

Boston M & S J, August 22 1849

MASSACHUSETTS MEDICAL SOCIETY



DEATHS

ALLEN — Harold M. Allen, M.D., of Lawrence, died July 3. He was in his sixtieth year.

Dr. Allen received his degree from Tufts College Medical School in 1913. He was a fellow of the American Medical Association.

His widow, a son and a daughter survive.

CLARK — Thomas F. Clark, M.D., of Taunton, died July 24. He was in his eighty-second year.

Dr. Clark received his degree from Harvard Medical School in 1901. For twenty years prior to his retirement in 1939, he served as head of the tuberculosis clinic for the city of Taunton. He was a charter member of the Bethlehem Home Corporation and was its first physician. He was a fellow of the American Medical Association.

His sister, three nieces and a nephew survive.

MATHEWS — Robert F. Mathews, M.D., of Worcester, died July 17. He was in his sixty-ninth year.

Dr. Mathews received his degree from University of Pennsylvania School of Medicine in 1905. He was a member of the American Urological Association and a fellow of the American Medical Association.

His widow survives.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

PERKINS — Frank B. Perkins, M.D., of Manchester, died on June 21. He was in his ninety-fourth year.

Dr. Perkins received his degree from Dartmouth Medical School in 1877. He was the oldest living member of the Society.

A son survives.

SWEENEY — Frederick C. Sweeney, M.D., of East Jaffrey, died on June 22. He was in his eightieth year.

Dr. Sweeney received his degree from University of Vermont College of Medicine in 1895. He was a fellow of the American Medical Association.

Three sons, two daughters and sixteen grandchildren survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

APPOINTMENT

James A McComb, D V M, has been appointed acting director of the Division of Biologic Laboratories, Massachusetts Department of Public Health. Dr McComb succeeds Dr Geoffrey Edsall, who has accepted the position of professor of bacteriology at Boston University School of Medicine.

Dr McComb, who has been with the Department for twenty-two years, entered the Division of Biologic Laboratories as assistant bacteriologist and a year later was appointed senior bacteriologist. He has served as assistant director of the Division since 1942.

A veteran of World War I, Dr McComb served in the Army as a sergeant in the field artillery. He was a lieutenant in the Army Reserve Corps for nine years.

He is a member of the American Veterinary Medical Association and the American Public Health Association.

RECOMMENDED PRACTICES FOR THE CONTROL OF POLIOMYELITIS

In view of the current prevalence of poliomyelitis, the Department and the Committee on Public Health of the Massachusetts Medical Society have endorsed a list of practices for the control of the disease. These practices, which were formulated by the National Conference on Recommended Practices for the Control of Poliomyelitis, held in Ann Arbor, Michigan, June, 1949, and are sponsored by The National Foundation for Infantile Paralysis, Inc., are in substance as follows:

THE DISEASE

Recognition of the Disease

Poliomyelitis is a highly prevalent infection of which only a small fraction of the cases is clinically identifiable. In its recognizable form it is an acute illness, usually febrile, with early varying symptomatology, but usually with headache and almost always a characteristic stiffness of the neck and spine that justifies an examination of the spinal fluid. In about half such cases a lower neuron paralysis develops in the first few days of illness, which shows a marked tendency for spontaneous improvement after it has reached its height. If the patient is first seen after the acute stage has passed, the diagnosis depends upon detection of a flaccid paralysis characteristically irregular in its involvement of muscle or muscle groups. Diagnosis in nonparalytic cases depends upon detection of a clinical picture compatible with the illness, plus the demonstration of a moderate increase in cells in the spinal fluid. A form of illness presumptively poliomyelitis (abortive) presenting only vague symptoms and without signs referable to the central nervous system is of frequent occurrence during epidemics.

Etiologic Agent

The poliomyelitis virus is the etiologic agent. Several immunologically distinct types have been identified.

Source of Infection

The pharyngeal and fecal discharges of infected persons, frequently those not suffering from a clinically recognized attack of the disease, constitute the source of infection.

Mode of Transmission

Close association with infected persons accounts for the great majority of cases. Outbreaks attributable to milk have been rare and limited. Although flies have been found to be contaminated with the virus, there has been no reliable evidence of spread by insects, water, food or sewage.

Incubation Period

Usually 7 to 14 days (May be from 3 to 35 days).

Period of Communicability

Apparently the period of greatest communicability is covered by the latter part of the incubation period and the first week of the acute illness.

Susceptibility and Immunity

Susceptibility to infection is general. Immunity is acquired by infection which may have been clinically inapparent. The duration of immunity is unknown, but second attacks are rare.

Prevalence

Infection is prevalent throughout the world. Paralytic cases have been apparently more frequent in the temperate zones. It occurs both sporadically and in epidemics at irregular intervals, with the highest incidence in summer and early fall. In the United States an annual incidence of 10 paralytic cases per 100,000 population is ordinary, but there is a wide variation in incidence from year to year and region to region. Children from 1 to 16 years of age are more frequently attacked than adults. In several countries, including the United States, older children and young adults constitute a higher proportion of reported cases than formerly. Even during epidemics the incidence of paralytic cases has rarely exceeded one per thousand population.

Methods of Control

- (a) Preventive measures none.
- (b) Through the infected person, contacts and environment.

Recognition of the disease by clinical manifestations assisted by microscopic and chemical examination of the spinal fluid if lumbar puncture is performed, and reporting it. In reporting, paralysis or its absence should be specified. A clear separation between these two groups of cases as reported permits a closer comparison of incidence between localities and with past experience.

Isolation for one week from date of onset, or duration of fever if longer.

Concurrent disinfections: nose and throat discharges and feces are infectious and should be disposed of as quickly and safely as possible. Articles soiled therein should be promptly disinfected.

Terminal disinfection none.

Quarantine: quarantine is of unproved value. Modified quarantine restricting the movement of intimate contacts for 7 to 14 days may be desirable in certain circumstances. (In Great Britain 21 days of exclusion from school of child contacts is required.)

Active immunization: there is none, and passive immunization is not recommended.

Investigation of source of infection: this consists of the search for and expert diagnosis of sick children to locate unrecognized and unreported cases of the disease.

- (c) Epidemic measures

General notice to physicians of the prevalence or increase of incidence of the disease, description of usual characteristics of the onset and the necessity for diagnosis and medical care, particularly for bed rest of patients, and information to the public at large on similar matters.

Isolation in bed of all children with fever, pending diagnosis.

Education in such technic of bedside nursing as will prevent distribution of infectious discharges to others from patients isolated at home

Protection of children so far as practicable against unnecessary contact with persons other than their usual associates

Postponement of elective nose or throat operations or dental extractions

Avoidance of excessive physical strain (for example, violent exercise) in children during an epidemic or in case of known exposure

Avoidance of unnecessary travel and visiting, especially of children, during a high prevalence of the infection

THE PATIENT

Reporting

All obvious and suspect cases should be promptly reported. As soon as possible all these cases should be classified as paralytic or nonparalytic. Cases which are finally diagnosed as presumptive (abortive) poliomyelitis should not be included in the final tabulation of cases by the health officers. For the guidance of health officers and physicians the following is proposed:

Diagnostic criteria of paralytic or nonparalytic poliomyelitis should generally include three or more of the following:

- History compatible with poliomyelitis
 - Fever
 - Stiff neck or stiff back or both
 - Ten to 500 cells per cc. of spinal fluid taken during the acute or early convalescent period of the disease
 - Spinal-fluid protein elevated above normal limits
 - Demonstrable muscle weakness or paralysis
- Cases that present only a history compatible with poliomyelitis, and fever, should be classified as presumptive (abortive) poliomyelitis.

Paralytic cases are defined as those in which definite weakness or paralysis has been detected and has persisted during at least two examinations with an interval of at least several hours. Results of an examination for paralysis of muscles of the extremities or trunk may be very unreliable during the period of muscle tenderness or "spasm."

Hospitalization

- (a) Admission to general hospital
Patients with acute poliomyelitis, or presumed to have acute poliomyelitis, are admissible to a general hospital provided that appropriate isolation precautions are employed. No special isolation or "pest" facilities are necessary.
- (b) Nursing care
Special-duty nurses should be employed with regard only to the medical condition of the patient, and to the number of patients they can properly handle.
- (c) Isolation technic in hospitals
The isolation procedures used for the care of acute poliomyelitis patients are similar to technics used in the hospital care of other communicable diseases, namely:

Segregation of patients having the same disease, preferably in single rooms or small wards. Patients can be cared for in large wards.

Washing of linen in the hospital laundry. Ordinary precautions for handling articles from infected persons are sufficient.

Sterilization of eating utensils after use.

Availability of toilets or hoppers in each room, small ward or large ward.

Availability of hand-washing facilities in each room, small ward or large ward.

Use of gowns by physicians when examining a patient and by nurses when caring for a patient, particularly while bedpanning.

Disposal of excreta of patients by placing in toilet or hopper as soon after passage as possible. The bedpan should be washed out if the utensil is used for a single patient, but when used in wards bedpans should be sterilized each time the utensil is used. No special treatment of feces from poliomyelitis patients is necessary.

Hand washing with ordinary soap and water should be practiced following examination of patients and after bedpanning a patient.

When toilet or hopper is situated outside the room or ward, a single pan should be covered and the contents disposed of as above. Multiple pans are best cared for by being placed on a cart and transferred to the disposal unit.

(d) Care at home

Patients may be cared for at home if home facilities and medically supervised care are adequate, or may be discharged to such home when there is no medical indication for further observation or treatment in the hospital.

Admission to or care in a hospital for isolation purposes only is not usually indicated.

(e) Care of suspect cases

It is recommended that suspect cases when admitted to a hospital should be segregated when possible from known cases until the diagnosis has been established or the patient is discharged as well.

(f) Importation of patients

In order that the best possible facilities may be used for the care of cases of poliomyelitis, patients may be sent from their own home communities to a hospital in another community. The available evidence indicates that such importation of patients into a hospital in a community where poliomyelitis is not prevalent does not effect the incidence of the disease in the hospital community.

(g) Transportation of patients

Transportation of patients from one health jurisdiction to another may be carried out under proper conditions, such as transportation in an ambulance or a private vehicle. A common carrier should not be used. Transfer should be carried out with the knowledge and the consent of the health officers in the jurisdiction to and from which the patient is being transferred.

No special treatment of ambulances after their use by poliomyelitis patients is necessary.

THE COMMUNITY

These recommendations were formulated with the emphasis on avoiding the possible effect of disturbing or altering unnecessarily the normal pattern of life in the community. Whatever is done to upset the usual routine of children in a household or adults in their occupations is likely to bring more trouble than good.

Schools

Public and private schools should not be closed during an outbreak of poliomyelitis, nor their opening delayed, except as noted below.

The closing of schools, or the delay of their opening, has not affected the course of outbreaks of poliomyelitis, moreover, such action has often resulted in panic on the part of the public. The decision to open school as usual should be announced well in advance jointly by the superintendent of schools and the health officer, in collaboration with the local medical society.

Early in the season the state departments of education and public health should issue a joint statement to which local authorities can refer for support. This statement should be issued in collaboration with the state medical society.

Exceptions

Schools to which children are transported in busses from widely separated areas may be delayed in opening if such action will prevent other close contacts among children. If these schools are not opened such action is justifiable only when other close contact among these children is not permitted in such places as theaters, picnics, playgrounds, swimming beaches or Sunday schools.

Boarding schools (excluding colleges and universities) should delay opening sessions if an outbreak of poliomyelitis exists in the area where the school is located and if the children are thus prevented from coming into the area from regions where the disease is not prevalent.

Nursery schools may be continued or closed depending upon the particular circumstances. Parents, if both are employed, may prefer to send their children to a nursery school. Parents who have facilities at home to limit contacts of young children with other children should be encouraged to keep preschool children at home.

Camps

Summer camps should be opened as usual if there is no outbreak of poliomyelitis in the area in which the camp is located.

Children should not be admitted from areas where an outbreak exists.

Inasmuch as there is no evidence that retention of children in camps where poliomyelitis exists leads to increased hazard, and that dismissal from camps may lead to spread to other communities, it is further recommended that if a case of poliomyelitis occurs in a camp the following procedures be instituted.

Retention of all children and staff at the camp for 14 days after the last contact with the case or until the usual closing date of camp.

Modified and supervised activity to prevent excessive exercise and undue mixing in group activities.

Careful medical checkup on all children daily.

Isolation of all children with fever or any suspicious signs and symptoms.

Discontinuance of admission of new children to camps in which poliomyelitis cases have been recently diagnosed.

Day camps should follow the same recommendations as those above pertaining to schools.

Places of Recreation and Amusement

It is recommended that health officers do not take action to close or prevent the operation of places of recreation or amusement, such as fairs, circuses, theaters, swimming pools or beaches, provided these are properly operated. However, the attendance of children at such places should be discouraged.

Any theoretical advantage that might be gained by closing such facilities is offset by the undesirable results of disruption of community life.

MIDDLESEX COUNTY			
Cambridge	Cambridge City Hospital	1 adult	—
Everett	Whidden Memorial Hospital	1 infant	—
Framingham	Cushing General Hospital	1	2
	Framingham Community Hospital	1	—
	Framingham Union Hospital	1	—
Lowell	St. John's Hospital	—	3
Malden	Malden Hospital	1	—
Newton	Newton Wellesley Hospital	—	1

ORFOLK COUNTY			
Quincy	Quincy City Hospital	1 adult	1
Wellesley	Wellesley Convalescent Home	1 infant	2

PLYMOUTH COUNTY			
Brockton	Brockton Hospital	1	—
Middleboro	Lakeside State Sanatorium	2	3

SUFFOLK COUNTY			
Boston	Beth Israel Hospital	2	—
	Boston City Hospital	7	3
	Carney Hospital	1	—
	Children's Medical Center	3†	10
	Haynes Memorial Hospital	6	3
	Massachusetts General Hospital	6	3
	New England Baptist Hospital	1	—
	Peter Bent Brigham Hospital	1	1
	St. Elizabeth's Hospital	1	—
	Veterans Administration Hospital (West Roxbury)	1	—
Chelsea	Chelsea Memorial Hospital	1	—
	Chelsea Naval Hospital	1	—
Revere	Revere General Hospital	1	—
Winthrop	Winthrop Community Hospital	1	—

WORCESTER COUNTY			
Fitchburg	Burbank Hospital	1	—
Gardner	Henry Heywood Memorial Hospital	1	—
Worcester	Belmont Hospital	1	—
	Memorial Hospital	1	—
	Worcester City Hospital	3	—

*List compiled jointly by the Massachusetts Department of Public Health and the National Foundation for Infantile Paralysis.

†Also 4 patient respirator room.

When called by a physician desiring assistance in diagnosing poliomyelitis in the acute stage, the fees of the following consultants will be paid by the county chapters of the National Foundation for Infantile Paralysis.

LOCATION OF RESPIRATORS AND HOT PACK MACHINES IN MASSACHUSETTS*

CITY OR TOWN	LOCATION OF EQUIPMENT	RESPIRATORS	HOT PACK MACHINES
BARNSTABLE COUNTY			
Hyannis	Cape Cod Hospital	1	1
BERKSHIRE COUNTY			
North Adams	North Adams Hospital	1	—
Pittsfield	House of Mercy Hospital	3	5
BRISTOL COUNTY			
Attleboro	Sturdy Memorial Hospital	1	2
Fall River	Fall River General Hospital	1	3
	St. Anne's Hospital	1	—
	Truesdale Hospital	—	1
	Union Hospital	2	2
New Bedford	St. Luke's Hospital	1 adult chest	2
		1 infant	—
Taunton	Morton Hospital	1	—
ESSEX COUNTY			
Beverly	Beverly Hospital	2	1
Danvers	Hunt Memorial Hospital	1	—
Haverhill	Hale Hospital	1	—
Lawrence	Lawrence General Hospital	2	1
Lynn	Lynn Hospital	2	1
Newburyport	Anna Jaques Hospital	1	1
Peabody	J. B. Thomas Hospital	1	1
Salem	Salem Hospital	3	1
FRANKLIN COUNTY			
Greenfield	Greenfield Isolation Hospital	1	1
HAMPDEN COUNTY			
Holyoke	Holyoke Hospital	1	2
Springfield	Health Department Hospital	2	1
HAMPSHIRE COUNTY			
Northampton	Cooley-Dickinson Hospital	1 adult	1
		1 infant	—

CONSULTANTS FOR THE DIAGNOSIS OF ACUTE POLIOMYELITIS

BOSTON	
DR. WILLIAM BLANKENBAG	Spinwall 7 9250
300 Longwood Avenue	
DR. LOUIS WEINSTEIN	Spinwall 7 5750
296 Allston Street, Brighton	
BEVERLY	
DR. ALLEN M. HILL	Beverly 4310
1 Monument Square	
GREENFIELD	
DR. MERRITT B. LOW	Greenfield 6832 (office)
31 Federal Street	6775 (home)
DR. ALEXANDER S. NADAS	Greenfield 6992 (office)
78 Federal Street	7647 (home)
	If no answer 5441
HOLYOKE	
DR. GEORGE D. HENOLSON	Holyoke 2-8577 (office)
176 Chestnut Street	2 9466 (home)
	If no answer 9611
LAWRENCE	
DR. A. ASH	Lawrence 2 9375
281 Haverhill Street	If no answer 2 5221
LYNN	
DR. MAURICE T. BRIGGS	Lynn 3-0223
7 Lynn Shore Drive	
MEDFORD	
DR. WALLACE J. NICHOLS	Medford 6-0842
116 Forest Street	
MELROSE	
DR. RALPH W. DAFFINCE	Melrose 4-4100
8 Porter Street	
NEW BEDFORD	
DR. CHARLES S. LIPSITT	New Bedford 2 1442
337 Union Street	
DR. GEORGE W. STABBUCK	New Bedford 2-6277
34 Arnold Street	

NORTHAMPTON	
DR. CLAIKE C. MAXWELL 16 Center Street	Northampton 857W
PITTSFIELD	
DR. JAMES E. BRESLIN 74 North Street	Pittsfield 2-3389
DR. GEORGE P. HUNT 131 East Housatonic Street	Pittsfield 6820
DR. FLOYD R. SMITH 18 Bank Row	Pittsfield 2-5253 If no answer 2-1551
QUINCY	
DR. MARION L. SLEMONS 195 Upland Road	GRanite 2-4940
SALEM	
DR. ROBERT T. MOULTON 39 Warren Street	Salem 2904
SPRINGFIELD	
DR. NORMAN A. POKORNY 23 Maple Street	Springfield 6-1721 If no answer 6-7241
WORCESTER	
DR. JACOB BREIN 796 Pleasant Street	Worcester 2-4344
DR. ROBERT D. COX 48 Kenwood Avenue	Worcester 2-1735
DR. ALFRED S. O'CONNOR 390 Main Street	Worcester 3-6557

CORRESPONDENCE

ACADEMY OF GENERAL PRACTICE

To the Editor On May 26 an editorial in the *Journal* extolled the virtues of the American Academy of General Practice and the institution of a Massachusetts Chapter.

To be eligible for membership in the Academy a candidate must be a graduate of an approved medical school and have other qualifications. Several of my confreres have reminded me that the Massachusetts Medical Society and the American Medical Association grant membership and fellowship to graduates of unapproved medical schools in this Commonwealth. It would seem, then, that an Academy has been established that is not open to every reputable doctor who is qualified for membership in the organizations that sponsor said Academy. If this is not talking out of both sides of our mouths, what is?

Those of us who take responsibilities in medical organization cannot help but react to this challenge of our organization to intellectual honesty. We have seen hospitals that use the authority of the American Medical Association for their internships flagrantly disregard rulings of this same American Medical Association that helps keep them in business. Is it any wonder that individual members do not trust their organization? Is it any wonder that a sizable percentage of our membership would just as soon trust the domination of social workers and politicians as they would us?

Of course Massachusetts has a little different situation but that is no reason why we do not revolt about the point taken in this communication. Sometime this line of reasoning could lead to a qualification as to when, where, and why we were born. Those who might be considered radical in feeling the thoughts expressed here are really tremendously conservative in that they want to protect upright and hard-working, competent fellow practitioners and I am sure we would suggest that in this fight for our lives and existence, the medical profession in its organization still has not acquired the broad and liberal viewpoint that should be one of its most valuable assets.

W A R CHAPIN, M D

121 Chestnut Street
Springfield, Massachusetts

Dr Chapin's letter was submitted to Dr James G. Simmons, secretary of the Massachusetts Chapter of the American Academy of General Practice, who offers the following reply:

Dr Chapin has raised a number of questions about the American Academy of General Practice that I believe I can answer to his satisfaction.

The American Academy of General Practice is an entirely independent organization, it is not a subsidiary of the American Medical Association, nor is it connected with any state medical society. It was founded by a group of general practitioners because it appeared that there was a need for such an organization to advance the interests of the family physicians, and give them greater opportunities for education, both undergraduate and postgraduate.

However, it has had the full co-operation of the American Medical Association from the beginning. Dr Paul A. Davis of Akron, Ohio, a member of the House of Delegates and chairman of the Section on General Practice of the American Medical Association, was appointed as its official representative at the original founding meeting in June, 1947. He became the first president of the Academy.

The Board of Trustees of the American Medical Association continues to co-operate through a co-ordinating committee to which the American Medical Association appoints three members representing the Board of Trustees, the Council on Medical Service and the Council on Medical Education and Hospitals.

Whereas the by-laws of the American Academy of General Practice provide that a candidate shall be a graduate of an approved school, the same by-laws give the board of directors of each state chapter the right to make exceptions to this rule under special circumstances.

Acting under this provision most of the state chapters have taken into their organization a number of graduates of other schools on the basis of their individual qualifications, their standing in their communities and the recommendations of their fellow practitioners. It is believed that the Academy can thus best carry out its purpose of raising the quality of general medical practice throughout the country. We believe that graduates of all schools can be helped by the Academy and that they in turn can help the Academy to become a great force for good in the medical community.

If your correspondent would like any further information about the Academy, the officers of the Massachusetts Chapter would be very happy to talk with him personally or correspond with him in further detail.

JAMES G. SIMMONS, M D, Secretary

30 Myrtle Avenue
Fitchburg, Massachusetts

THE MORAL ISSUE

To the Editor Dr Leo Alexander's account of German "killers in white" in the July 14 issue of the *Journal* warns that we in this country must be on guard against a policy of inadequate treatment of dependent sick persons, mistreatment forced on doctors by an economy-minded public. But we must keep in mind that cruel and unmerciful treatment can be meted out in the very name of mercy and of religion. The atrocities committed by German doctors were acute, ours are long lasting.

Doctors who are custodians of children with undeveloped or misformed brains deny these pitiful creatures the mercy of natural death from infection. They give prophylactic inoculations and the wonderful new germ-killing drugs, and thereby force on these helpless creatures an indefinite number of miserable years. Their drawn-out misery is shared by their parents and by the many patients who could be helped but cannot gain entrance to our hopelessly clogged institutions.

I speak only of the near hairless and mindless creatures beyond reach of any medical miracle, now or ever. Doctors in charge cannot exercise their natural feeling of humanity and mercy because of the pressure of unknown popular sentiment—ignorance that doctors in general make no effort to lighten "Religious" hands raised in protest against the infectious friends of the permanently defective are, many of them, stained with the cruelly tortured blood of the Inquisition. "Be ye merciful" is a broad and compelling command.

WILLIAM G. LENOX, M D

Boston

To the Editor One of the most pertinent articles appearing in the *Journal* in recent months was in the July 14 issue, by Dr Leo Alexander, entitled "Medical Science Under Dictatorship."

One is prompted to gratitude and applause that in some quarters, at least, beyond our preoccupation with pathophysiology and health insurance, the essential values that identify a doctor have been recalled.

Dr. Alexander's careful analysis indicates what happens to the physician when he takes materialism from society and turns to view his patient. He soon embraces the attitude of "scientism" as his philosophy. The person who is the doctor's patient becomes an "organism." His tired sclerotic arteries, on which depend the perilous balance of a family livelihood, give him a number in a statistical series. Because the patient is a "case," the doctor feels no more responsibility beyond giving him a "controlled study," and the medical conscience is at peace if it sends him off with the "latest form of therapy." From this materialistic outlook on man, the level of morality of the practicing physician, such as it is, is likewise materialistic and his code then becomes "usefulness to society," utilitarianism, and rank sentimentality.

The science of medicine is one thing. The profession of medicine is quite another. The business of a practicing physician is undeniably linked to the Christian virtue of Charity. This implies the truth of man created by God. Herein lies the inherent dignity of man. From where else comes the logic of the argument against the practice of euthanasia? The hydrocephalic or the mongol may not be apparently "useful to society," but he is "useful" to God, by virtue of being His creature. Unless doctors abandon their subtle omnipotency, and realize that the values that define their profession are Christian values, their art will be reduced to a technique. Where do doctors meet this "scientism"? At the beginning—for four full years in medical school. As a recent graduate, I can vouch for the difficulty of a medical student's viewing man as anything more than viscera, muscle groups and "integrated reflexes." The honest respect that he has for his instructor's learned outline of anatomy and physiology is easily shifted to an identification with his materialistic innuendoes and—the "organism." In all the wealth of his clinical teaching, where is he told of the practice of medicine and the values underlying it? Exhortations to "treat the patient as a whole" are not enough. He must gain an idea why the patient is worth treating at all. I urge you, therefore, to look again at the medical schools.

J. JERROLD APPELGARTH, M.D.

The Roosevelt Hospital
New York City

To the Editor: You are very much to be commended for publishing Dr. Leo Alexander's excellent article, "Medical Science under Dictatorship." It not only is well written and scholarly, but does the long neglected task of pointing out fallacies in our own attitude toward medical practice.

It is reassuring to know that there are still some physicians who care about the moral aspects of the patient-doctor relation. How easy it is for us to become callous to the individual in order to perfect some technique supposedly for "the common good"! I hope that many of your readers will take his message to heart and that his acute perceptions will receive wide dissemination.

I hope, too, that this will not be the last article dealing with what may be called the philosophy of medicine. In the light of eternal values, this is really more important than the technical advances we are so careful and so prompt in reporting.

Congratulations, again, to you and to Dr. Alexander.

JAMES E. BOWES, M.D.

89-05 Hollis Court Blvd
Queens Village 8, N. Y.

THE OTHER SIDE

To the Editor: Having in mind the declaration by the Minister of Health, Mr. Bevan, in the House of Commons May 5, 1949, that "We cannot, obviously, without the most careful consideration and legal safeguards, push needles into people whether they want to have them pushed in or not," we maintain in reply to your editorial of July 7 entitled "Strange Bedfellows" that we neither lose our perspective nor depart from our apparently laudable purpose when we maintain that the right of the individual to escape vaccination or other compulsory measures can be achieved without jeopardizing the common good.

The Bill of Rights is largely concerned with the protection of the rights of minority groups, and the effect of these safeguards that are thrown around minority groups serves to provide the greatest possible protection that could be provided to majority groups. Obviously, under a system of voluntary vaccination, the unvaccinated cannot possibly expose to disease those who have been vaccinated against the disease. Since there were only 59 cases of smallpox reported in the United States in 1948 and since vaccination is not generally required in the majority of the states, the prevalence or absence of smallpox is apparently more influenced by so-called "unknown factors" than it is by compulsory vaccination in any form.

We wish to thank you for stating the purpose of the Bureau correctly and for presenting an accurate summary of our Bulletin 429.

H. B. ANDERSON, Secretary

Citizens Medical Reference Bureau, Inc.

1860 Broadway
New York City

DEPRIVATION AND RESTORATION OF LICENSES

To the Editor: At the meeting of the Board of Registration in Medicine held June 16, it was voted to revoke the registration of Dr. Earl G. Hersey of Milton.

At the meeting of the Board of Registration in Medicine held July 12, it was voted to restore the registration of Dr. Glenn F. Muntz, 6 St. Charles Street, Boston.

GEORGE L. SEHANT, M.D., Secretary
Board of Registration in Medicine

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Skin Diseases. A manual for practitioners and students. By James Marshall, M.D., B.S., M.R.C.S., L.R.C.P., consulting dermatologist, Central Middlesex Hospital, and director of venereal diseases clinic, Royal Northern Hospital, London. 8", cloth, 363 pp., with 8 color plates. London: Macmillan and Company, Ltd., 1948. \$7.50.

In this new manual the common diseases are given extended treatment, but the whole field of dermatology is covered to some extent. Syphilis is included, as well as the nails, hair, sweat and sebaceous glands, and the mucous membrane. There is a short chapter on tumors of the skin. Recent advances in therapy have been included to bring the manual up to date. The text is well organized, and the volume well published. There is a good index.

Irregular Discharge. The problem of hospitalization of the tuberculous. Prepared by William B. Tollen, Ph.D., Research Division, Co-ordination Service, at the request of the Department of Medicine and Surgery, Veterans Administration. 8", paper, 64 pp. Washington: Veterans Administration, 1948. 20c. VA pamphlet 10-27.

In this small pamphlet a comprehensive study is made of the tuberculous patients in veterans hospitals who "walked out" or were lost track of before their required hospitalization and treatment had been completed (technically known as "irregular discharges"). Over 50 per cent of the discharges from Veterans Administration hospitals of living tuberculous patients were irregular, and only 45.6 per cent were regular. The patients with irregular discharges were still injuriously affected by tuberculosis and required further hospitalization. The problem as visualized is basically a social one for the community at large.

Synopsis of Psychosomatic Diagnosis and Treatment By Flanders Dunbar, M D With the assistance of Jacob Arlow, M D, and others, and members of the staff of the departments of medicine and psychiatry, Columbia-Presbyterian Medical Center, New York City 12°, cloth, 501 pp St Louis C V Mosby Company, 1948 \$6 50

This manual is written primarily for the general practitioner, and is intended to be a guide to the newer methods of diagnosis and treatment. An attempt has been made to follow Osler's outline, with the addition of new material to the sections on differential diagnosis and treatment. The text is well arranged, and the various chapters are written by specialists in their fields. There is a long bibliography and an extensive index. The volume is well published and should prove useful as a ready reference source.

Primary Anatomy By H A Cates, M B, professor of anatomy, University of Toronto 8°, cloth, 478 pp, with 392 illustrations Baltimore Williams and Wilkins Company, 1948 \$6 00

This new treatise on anatomy is written for nonmedical students, including nurses, physiotherapists, occupational therapists, physical educationists and other interested persons. The treatment is by systems of the body, rather than by regions, because this method is easier for the beginner. The illustrations are schematic drawings prepared especially for these groups of students. The material is well arranged, and the book well published. The type is particularly good. There is an extensive index. The volume should prove valuable to nonmedical persons.

Emergencies in Medical Practice Edited by C Allan Birch, M D, F R C P, physician, Chase Farm Hospital, Enfield 8°, cloth, 468 pp, with 113 illustrations Baltimore Williams and Wilkins Company, 1948 \$7 00

This composite work is written by nineteen specialists who have contributed articles in their special fields. The material is confined solely to emergencies of a medical character. The whole field of medicine is covered, and there are special chapters on emergencies in industrial medicine, at sea and in the air, and on medicolegal and other nonclinical emergencies. There is a good index. The volume is well published, but the use of a heavy filled paper is not justified by the two essential color plates. These could have been tipped into a lighter volume. The text was printed in Great Britain.

Hallmarks of Mankind By Frederic W Jones, D Sc, M B, B S, F R S, F R C S, Sir William Collins Professor of Human and Comparative Anatomy, Royal College of Surgeons of England 8°, cloth, 86 pp, with 23 illustrations Baltimore Williams and Wilkins Company, 1948 \$2 50

This small volume contains the subject matter of two lectures delivered by the author in 1947. It expresses his theories of the evolution of man, which he has held for over thirty years. His two main contentions are that man, "considered solely from the point of view of structure, is an extremely primitive type" and that "more primitive in basal structure than the living monkeys and apes, man has his own remarkable structural specializations that distinguish him from all other mammals and appear to be his ancient hallmarks." The text is interspersed with pertinent illustrations. The publishing is excellent. The printing was done in Great Britain. The book is a necessary source of information to all persons interested in the subject of evolution.

The Surgery of the Stomach and Duodenum By T H Somervell, M A, M B, B Ch (Cantab), F R C S (Eng), surgeon-in-charge, London Mission Hospital, Neyoor, S India, and examiner in surgery to the University of Madras 8°, cloth, 546 pp, with 231 illustrations Baltimore Williams and Wilkins Company, 1948 \$11 00

The author of this special work on surgery had an extensive experience in India, where gastric and duodenal diseases are very prevalent. He believes that ligation of the gastric vessels and even vagotomy are preferable to gastrectomy for the average surgeon. His work is based on the literature of the subject, as well as his vast experience. Likewise, Dr Somervell is impressed with the future of the transthoracic operation for surgery of the upper abdomen and especially the trans-

diaphragmatic method of Dr Gardham, of London. These operations are described in detail in the chapter on esophago-gastric conditions. The text is well organized. The preliminary chapters are devoted to embryology, anatomy, physiology, pain, diagnosis and operative methods in general. The following chapters deal with the various diseases and conditions of the stomach and duodenum. There is a special chapter on the gallbladder and pancreas in relation to gastroduodenal surgery. Short lists of selected references are appended to the various chapters, and a bibliographic index lists the authors of the references in alphabetical order. There is also a good index of subjects. The illustrations were mostly drawn by the author. The text was printed in Great Britain, and the type and printing are excellent. The book should be in all medical libraries and available to all surgeons interested in gastric and abdominal surgery.

Medical Manual By William R Feasby, M D, medical assistant to the superintendent, The Toronto Western Hospital, and lecturer in physiology, University of Toronto 16°, cloth, 162 pp Toronto University of Toronto Press, 1948 \$2 25

This small manual is intended primarily for senior students, interns and nurses. The text is intentionally brief, but an effort has been made to include the information needed for everyday use. The greater part of the text is devoted to materia medica, diet and clinical methods. There is a special chapter on legal considerations. There is a list of common diagnoses and a good index. The manual compares favorably with similar publications.

Physicians' Federal Income Tax Guide For the preparation of 1948 returns and 1949 estimates By Hugh J Campbell and James B Liberman 1948-49 edition 4°, paper, 96 pp Great Neck, New York Doniger and Raughley, Incorporated, \$2 50

This valuable manual should be owned by every physician. It explains in detail how to make out tax returns and estimates. The tables of professional deductions, nontaxable receipts and nonprofessional deductions are especially valuable. The pamphlet is well published.

Allergy to Cottonseed and Other Oilseeds and Their Edible Derivatives. Excerpts from testimony before the administrator, Federal Security Agency. In the matter of fixing and establishing definitions and standards of identity for mayonnaise, French dressing, and related salad dressings (docket FDC-51). Public hearing held at Washington, D C, November 18, 1947 and January 6 to 8, 1948 8°, cloth, 275 pp Memphis, Tennessee National Cottonseed Products Association, Incorporated, 1948 Free

This volume contains the testimony of 6 expert witnesses on allergy to cottonseed oil and other oilseed products, and of 2 other experts concerning relevant factors of vegetable-oil technology. The testimony was given at public hearings held before the Federal Security Administrator on November 18, 1947, and January 6-8, 1948, in the matter of fixing and establishing definitions and standards of identity for mayonnaise, French dressing and related salad dressing. The evidence presented had to do with allergy to edible oils. The edition was limited to 500 copies and presented to all medical schools in the United States and to selected medical and scientific libraries with the intention of making the volume available to all interested persons. It is not for sale.

The British Encyclopaedia of Medical Practice, Including Medicine, Surgery, Obstetrics, Gynaecology, and Other Special Subjects (Medical Progress 1948) Editor-in-chief, Rt. Hon Lord Horder, G C V O, M D, B Sc., F R C P, physician to the King, and consulting physician to St Bartholomew's Hospital 8°, cloth, 539 pp, with 5 illustrations London Butterworth and Co (Publishers), Ltd, 1948

This volume is the latest of a long series intended to portray the advances in medicine for the year 1948. It is issued to supplement the encyclopedia, and the series brings this large work up to date.

Clinical Urology Essentials of diagnosis and treatment By Lowrain E. McCrea, M.D., F.I.C.S., clinical professor of urology, Temple University School of Medicine, and attending urologist, Philadelphia General Hospital. Second edition. 8°, cloth, 503 pp., with 263 illustrations. Philadelphia: F. A. Davis Company, 1948. \$6.50.

The first edition of this book was published in 1946, and the demand for a new edition so soon is evidence of its soundness and popularity. The text, which has been brought up to date and in a large part rewritten, is based solely on the experience, practice and opinions of Dr. McCrea. The volume is well published. The type is excellent, making for easy reading. There is an extensive index. The use of a coated paper makes the volume rather heavy for its size. The book should be in all medical libraries and should prove useful to all physicians interested in urology.

Acta Radiologica Supplementum 65 Intussusception in Children. Diagnosis and therapy with barium enema By Hans Hellner. 4°, paper, 120 pp., with 50 illustrations and 6 tables. Lund, Sweden: Hakan Ohlssons Boktryckeri, 1948. Swed. Crowns 15.—

Supplementum 68 Carcinoma of the Tongue. A clinical study of 277 cases treated at Radiumhemmet, 1931-1942 By Folke Jacobsson. 4°, paper, 190 pp., with 24 illustrations. Stockholm: Esselte Aktiebolag, 1948. Swed. Crowns 20.—

Supplementum 69 A Pneumographic Study of the Temporal Horn. With special reference to tumours in the temporal region By Erik Lindgren. 4°, paper, 151 pp., with 239 illustrations. Stockholm: P. A. Norstedt and Sons, 1948. Swed. Crowns 25.—

Supplementum 70 Studies on Back-flow in Excretion Urography By Olle Olsson. 4°, paper, 80 pp., with 18 illustrations. Lund: Hakan Ohlssons Boktryckeri, 1948. Swed. Crowns 20.—

Supplementum 71 On the Transmission Through Skin of Visible and Ultraviolet Radiation By K. G. Hansen. 4°, paper, 106 pp., with 84 illustrations. Copenhagen, Denmark: Arnold Busck, 1948. Swed. Crowns 8.—

These supplements are all written in English and present the latest information on the subjects under consideration.

Language and Language Disturbances. Aphasic symptom complexes and their significance for medicine and theory of language By Kurt Goldstein, M.D. 8°, cloth, 374 pp. New York: Grune and Stratton, 1948. \$8.75.

This monograph on aphasia is divided into two main parts: the origin of aphasic symptoms, and case reports, pathologic anatomy, and treatment. The discussion of treatment is limited to twenty pages. The literature of the subject is referred to throughout the text. The material is well organized and well presented. The book is well published and should be in the reference collections of all medical libraries and available to all neurologists. There is a bibliography of 332 items, as well as indexes of authors and subjects.

The Shame of the States By Albert Deutsch. 8°, cloth, 188 pp., with illustrations. New York: Harcourt, Brace and Company, 1948. \$3.00.

In this small volume Mr. Deutsch presents a camera-documented story of conditions in the public mental hospitals in the United States. During a period of eighteen months the author visited thirty state hospitals from coast to coast, and found shocking conditions in many. On some of the visits the author was accompanied by news photographers, and some of the pictures taken are reproduced in the volume. In two chapters the United States Army's Mason General Hospital, at Brentwood, New York, and the Brooklyn State Hospital are described as two of the better hospitals, despite the overcrowding at Brooklyn. Mr. Deutsch conferred with many experts, who could not point to any hospital as being the best in the land. All had their deficiencies, but, according to the author, "the fact is that not a single state mental hospital in the whole country meets all the minimum standards of care and treatment, established twenty years ago by the American Psychiatric Association." The concluding chapters have to do with the efforts to remedy the existing deplorable conditions.

The Case Against Socialized Medicine. A constructive analysis of the attempt to collectivize American medicine By Lawrence Sullivan. 12°, cloth, 53 pp. Washington: The Statesman Press, 1948. \$1.50.

Mr. Sullivan, in this small book, presents in short chapters a historical account of socialized medicine. The story is based principally on the sworn testimony of witnesses appearing before committees of the House and Senate.

NOTICES

ANNOUNCEMENTS

Dr. Salvador Jacobs announces the opening of offices at 66 Rogers Avenue, Lynn, and 416 Marlborough Street, Boston, for the practice of neurology and general psychiatry.

Dr. Frederick Rosenheim, formerly associated with the Judge Baker Guidance Center, announces the opening of an office at 122 Commonwealth Avenue, Boston, on September 6.

Dr. Nathaniel M. Stone, of 371 Commonwealth Avenue, Boston, will continue the x-ray practice of his former associate, Dr. John W. Meachen, at 332 Pleasant Street, Malden. Offices will be open at both addresses.

Dr. George J. Warren announces the opening of an office at 55 Broad Street, Lynn, for the practice of urology.

MASSACHUSETTS STATE SOCIETY OF EXAMINING PHYSICIANS

A meeting of the Massachusetts State Society of Examining Physicians will be held on Wednesday, November 16, at 6:30 p.m., at the Harvard Club in Boston. Following the dinner, Dr. Fred Jostes of St. Louis, Missouri, will present a paper on rehabilitation.

All physicians are cordially invited to attend.

TRAINING IN PSYCHIATRY

The United States Public Health Service under the National Mental Health Act has approved a grant for a trainee in psychiatry at the Walter E. Fernald State School situated 8 miles from Boston. The stipend is level 5, or \$3000 per year. However, candidates at lower levels may be considered and the amount of the stipend adjusted to the level of the candidate's training. Training will be offered in mental deficiency, child psychiatry, and related psychiatric and neurological problems through supervised experience in the out-patient, in-patient, research laboratory, psychological, educational and social-service departments, as well as participation in staff meetings, seminars in basic psychiatry and neurology and in child psychiatry.

Applications including the candidate's qualifications or requests for further information should be forwarded to Dr. Malcolm J. Farrell, Superintendent, Walter E. Fernald State School, Waverley 78, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 6-10 American Congress of Physical Medicine Page xiii
issue of March 24

SEPTEMBER 8 Care of the Terminal Stage of Cancer Dr. John W. Spellman
Pentucket Association of Physicians 8:30 p.m. Haverhill

SEPTEMBER 28 New England Pediatric Society Page 136
issue of July 21

SEPTEMBER 28-30 Mississippi Valley Medical Society Page xi
issue of July 14

OCTOBER 3-MAY 19 Massachusetts Department of Mental Health
Postgraduate Seminar in Neurology and Psychiatry Page 286
issue of August 18

OCTOBER 11-15 American Society of Clinical Pathologists
Hotel Chicago

(Notices concluded on page xiii)

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MEDICAL CONSIDERATIONS IN THE CARE OF ELDERLY PATIENTS WITH HIP FRACTURES*

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BOSTON

IN SHARP contrast to the attitude of a few years back, hip nailing in aged people suffering from various medical disabilities has become accepted surgical practice. Penicillin, carefully controlled anesthesia, the use of blood and standard physiologic fluids, refinements of surgical technic and early ambulation have permitted feats of major surgery previously believed impossible, especially in the aged. In the cases of hip fracture, traction or a plaster spica was used by choice under the impression that operation was too great a risk in this age group. This attitude is now reversed, and nailing is performed to avoid the many evils of prolonged bed rest and traction, to diminish the burdens on an already overtaxed nursing staff and, most important, to lower an appalling mortality rate.

The serene course of some patients with even critical medical conditions both during and after operation has been surprising. With good medical care and follow-up study and careful selection of patients and time of operation, a satisfactory outcome is now expected. Nevertheless, some deaths have occurred postoperatively in patients who were judged acceptable for hip nailing—usually from conditions that were present before the operation or even the fracture. The most important medical factors, therefore, have not been emphasized in the literature on hip fracture. No criteria have been established regarding selection of the patient and the time of operation or what definite measures can be taken under specific circumstances to facilitate surgery or make it possible.

To clarify our thoughts in the matter with the purpose of holding operative mortality to a minimum we studied the records of 100 consecutive patients who had attained the age of seventy or over, who were treated on the Sixth Surgical Service, Boston

City Hospital for fracture of the hip. The periods of treatment were between November, 1944, and January, 1948. This was a period in which penicillin was in general use—a factor that, we believe, had an important bearing on the general clinical course. No attempt was made to include follow-up studies inasmuch as this paper deals with the medical care in the hospital until the patient is ready for discharge.

In this series, the operation of nailing was done by one of two methods—"open" in the operating room or by the so-called "closed" method under the fluoroscope. The first was more frequently used.

The patient was given light premedication and was transported to the operating room with the injured limb supported on a Thomas splint. Low spinal anesthesia of light dosage was given, and intravenous injection of saline solution was started and allowed to run slowly.¹ Two pints of blood were ready if needed. The fracture was reduced by a suitable method, a modified Leadbetter maneuver or, in the cases of some intertrochanteric fractures, traction with internal or external rotation. X-ray films taken with a portable apparatus were used to check the position. After skin preparation and draping, the upper femoral shaft was approached through a straight or curved lateral incision, deepened through fascia lata and vastus lateralis. Sufficient periosteum was elevated to permit insertion of two Bennett retractors. Fixation depended on the type of fracture and the judgment of the operator. Kirschner wires and x-ray films taken with a portable apparatus were used to find proper length and direction.

The "closed" method was performed in the dark room with the aid of the fluoroscope. Reduction may be checked by a film taken with the cassette placed in the viewing screen. Kirschner wires were then drilled across the fracture site through the prepared skin. An incision 2.5 cm. in length, was made down to bone around the correctly placed wire. A cannulated Smith-Petersen nail was threaded over the wire and driven home. This procedure

*Presented in part at the annual meeting of the American College of Surgeons, Committee on Fractures and Other Traumas, Boston, January 29, 1949, and at the Boston City Hospital postgraduate course in fractures conducted by Sir Reginald Watson Jones, May, 1948.

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§Instructor in orthopedic surgery, Harvard Medical School; surgeon-in-chief, Boston City Hospital; chief, Sixth Surgical Service, Boston City Hospital.

could be completed very often in thirty or forty minutes, which, together with the minimal operative trauma, constituted its chief advantage.

Postoperative care was aimed to get the patient either out of bed or moving about freely in bed as soon as possible, and as soon as strength and freedom from pain allowed. Sometimes a day or two after operation a woman in her middle eighties was up in a chair, surprised and smiling at how well she felt. Quadriceps exercises and knee motion were encouraged, daily check was made for common complications, especially calf tenderness, pain and foot edema. Again, when strength was sufficient, usually a matter of two or three weeks, the patient was allowed up in a walker and then on crutches under supervision. The foot on the injured side was placed on the floor, with very little or no weight bearing, to avoid the awkwardness of crutch walking with the hip and knee flexed.

Time of discharge depended on many factors, most of them social.

Seventy-two of the 100 patients were operated upon. Twenty-eight were treated conservatively either by traction or by application of a plaster spica. Conservative treatment was instituted be-

few hospital days. In the first group were good operative risks, in the second fair operative risks and in the third patients on whom operation was contraindicated.

Group I

In Group I we placed patients who, in spite of their age, were in good physical condition. They tolerated surgery very well and required only the usual preoperative and postoperative care. Unfortunately, this was a small group. In our series of 100 cases, 13 fell into this category. There was no mortality. The following case is typical.

E. Q., a 76-year-old woman, entered the hospital on December 5, 1946, with a history of having slipped and fallen on her porch on the day prior to entry. After this accident she noted pain in the left hip and inability to stand. Physical examination showed shortening and external rotation, with painful motion of the left hip. The lungs were clear, the heart was not enlarged, and the rate and rhythm regular, with a soft apical systolic murmur. The blood pressure was 140/70. Routine laboratory work was negative. X-ray study showed an intertrochanteric fracture of the left hip. The patient remained in excellent physical condition in Russell traction. On the 5th day a Smith-Petersen nail with a Thornton atachment was inserted uneventfully. Anatomic reduction was obtained. The postoperative course was uneventful, and the patient was discharged on the 17th hospital day, on crutches, to be followed at home by her own doctor.

Group II

Group II included patients who showed the scars of aging. They had underlying physical disabilities that required active and prompt medical treatment prior to operation, cautious anesthetic and operative handling and a close postoperative follow-up study. That hip fracture in the elderly is very often as much a medical as a surgical problem can be seen from the fact that 70 cases fell into this group.

Four patients in this group died. A typical case is as follows.

S. M., an 83-year-old woman, entered the hospital on April 12, 1947, with a complaint of pain in the right hip after a fall on the night prior to admission. She also gave a history of long-standing diabetes and hypertension. The diabetes had been treated with diet alone, but she had been taking digitalis intermittently for the past year. Physical examination revealed a well developed woman in no apparent distress. The lungs showed moist rales at both bases. The heart border was enlarged to the anterior axillary line, and there was a rough, Grade III systolic murmur. The blood pressure was 190/100. There was shortening and external rotation of the right leg. The urine showed an orange Benedict reduction, and the sediment was loaded with white blood cells. Examination of the blood disclosed a hemoglobin of 65 per cent and a white-cell count of 8600. The blood sugar was 250 mg., and the nonprotein nitrogen 42 mg. per 100 cc., and the carbon dioxide combining power 49 per cent. X-ray examination showed an intertrochanteric fracture of the right femur. The right leg was placed in Russell traction, and immediate attempts to restore cardiac compensation and regulate the diabetes were instituted. The patient was given penicillin and sulfadiazine to combat the urinary-tract infection. By the 16th hospital day the diabetes was under good control, all evidence of cardiac decompensation had cleared, and the urine sediment was normal. She was then operated upon under spinal anesthesia. Smith-Petersen nail with a Thornton plate was successfully inserted. The postoperative course was smooth, and she was out of bed on the 4th postoperative day and discharged from the hospital on the 58th hospital day on crutches.

TABLE 1 Medical Grouping of All Patients

GROUP	STATUS OF PATIENT	SURVIVALS	DEATHS	TOTALS
I	No detectable disease process	13	0	13
II	Mild to moderate reversible conditions	64	6	70
III	Severe, nonreversible conditions becoming worse	0	17	17

cause of personal choice of the attending surgeon, because of the nature of the fracture or because the patient was considered a poor surgical risk. Sixty-one had intertrochanteric fractures, and 39 fractures of the femoral neck. Of the patients operated upon, 13 died—a mortality of 18 per cent. In the group treated conservatively there were 9 deaths—a mortality of 32 per cent. The high mortality in this group reflects the fact that it included many poor-risk patients. The average time in the hospital prior to surgery was nine and four-tenths days. The patients operated on were out of bed, on the average, in twelve and five-tenths days, and those treated conservatively in forty-one days. The average hospital stay was forty-five days for the operated patients and seventy-seven days for those treated conservatively. These statistics differ little from reports of several other large clinics.²⁻⁸

No attempt has been made to correlate the type of fracture with the mortality.

We have found that our cases could be classified into three groups (Table 1), depending upon the amount and type of concomitant medical disability existing as observed during their first

Group III

Group III comprised patients with severe and extensive medical problems who, under adequate medical management, showed no evidence of improvement or were becoming worse under conservative treatment. The trauma of hip fracture tipped the balance in these elderly people in much the same manner that a bronchopneumonia becomes the terminal event in the elderly patient with cardiac disease. Seventeen patients fell into this group, 9 were operated upon, and 8 were treated conservatively, all died. The following case is typical.

H. E., a 77-year-old woman, entered the hospital on January 21, 1945. On the day of admission she had tripped and fallen on her right hip, sustaining a fracture of the right femoral neck. Physical examination showed an elderly, unco-operative woman in moderate pain. The lungs demonstrated bilateral moist rales at the bases. The cardiac border extended to the left, the sounds were of poor quality, and there were rough systolic murmurs at both apex and base. The peripheral arteries showed evidence of marked arteriosclerosis, and the eyegrounds consistent changes. The blood pressure was 160/110. There was shortening and external rotation of the right leg. The urine was normal. Examination of the blood disclosed a hemoglobin of 57 per cent and a white-cell count of 7200. The blood Hinton reaction was negative. The nonprotein nitrogen was 43 mg, and the fasting blood sugar 110 mg per 100 cc.

The patient was placed in Russell traction. When seen by a medical consultant shortly after admission she was found to be in marked congestive failure. She was placed on a salt-poor diet and given ammonium chloride, mercurpurin, digitalis and sulfadiazine. She did not improve under this regimen and became more and more unco-operative. Her course was downhill, cardiac failure persisting. A bronchopneumonia developed, and she died on the 22nd hospital day.

In our opinion operation would not have changed the outcome in this case.

TABLE 2 Conditions Existing before Operation in 72 Cases*

CONDITION	NO OF CASES	SURVIVALS*	DEATHS†
Cardiovascular disease	41	31	10
Decubitus ulcer	9	8	1
Renal tract infection	8	5	0
Anemia (severe)	7	7	0
Diabetes	7	4	3
Pneumonia	6	5	1
Previous cerebrovascular accident	6	6	0
Psychosis	6	4	2
Emphysema (pulmonary)	5	5	1
Prostatism	5	5	0
Cataracts	4	4	0
Urinary and fecal incontinence	3	3	0
Bronchiectasis	3	2	0
Obesity	3	2	0
Carcinoma of stomach	3	1	1
Colles fracture	2	2	0
Bilateral active pulmonary tuberculosis	1	1	0
Uremia and acidosis	1	0	1
Hypoproteinemia (severe)	2	1	1
Cachexia (extreme)	1	1	0
Rheumatoid arthritis	1	1	0
Reitman-cell sarcoma of pelvis	1	1	0
Pernicious anemia	1	1	0

*Total of 59 cases

†Total of 13 cases

Table 2 lists the recorded underlying diseases that, in various combinations, were found in the 72 patients undergoing operation. It is immediately

apparent that cardiovascular disease was the greatest complicating factor. Forty-one cases were diagnosed as either arteriosclerotic heart disease or hypertensive heart disease, or both. No cases of rheumatic or syphilitic heart disease were encountered, as might be anticipated in this age group. Ten of these 41 patients were in congestive failure. Other medical disabilities having a direct effect on the outcome were diabetes, pneumonia, uremia and psychoses.

Table 3 demonstrates the effect of congestive failure on the mortality and points out that the

TABLE 3 Arteriosclerotic and Hypertensive Heart Disease in 41 Patients Operated Upon

STATUS	NO OF CASES	SURVIVALS	DEATHS
Compensated	28	26	2
Congestive failure	13	5	8
Totals	41	31	10

mere presence of cardiac disease has little or no bearing on the general mortality rate, provided there is no failure.

Table 4 lists the complications following surgery. Conditions existing prior to surgery are not in-

TABLE 4 Complications Following Operation

COMPLICATION	TOTALS	SURVIVALS	DEATHS
Pneumonia	10	4	6
Phlebotrombosis or thrombophlebitis or both	11	9	2
Pulmonary embolism	2	0	2
Atelectasis	3	2	1
Circulatory failure (shock)	3	0	3
Uremia	2	0	2
Renal tract infection	4	4	0
Cerebrovascular accident	1	0	1
Ileus	3	1	2
Wound infection	4	4	0
Gangrene of involved extremity	2	0	2
Psychosis	5	2	1
Decubitus ulcer	7	5	2
Gastrointestinal hemorrhage (carcinoma of stomach)	1	0	1

cluded in this list. Noteworthy is the high incidence of pulmonary complications such as pneumonia, atelectasis and emboli. Circulatory failure developed in only 3 cases.

DISCUSSION

Preoperative Study

In medical evaluation certain points in the history and physical examination are of special concern.

History. One should determine, in eliciting the present illness, whether the trauma was a result of a simple accident, such as tripping or slipping, or whether the patient fell because of a "fainting spell." In this age group such spells are often due to serious

could be completed very often in thirty or forty minutes, which, together with the minimal operative trauma, constituted its chief advantage.

Postoperative care was aimed to get the patient either out of bed or moving about freely in bed as soon as possible, and as soon as strength and freedom from pain allowed. Sometimes a day or two after operation a woman in her middle eighties was up in a chair, surprised and smiling at how well she felt. Quadriceps exercises and knee motion were encouraged, daily check was made for common complications, especially calf tenderness, pain and foot edema. Again, when strength was sufficient, usually a matter of two or three weeks, the patient was allowed up in a walker and then on crutches under supervision. The foot on the injured side was placed on the floor, with very little or no weight bearing, to avoid the awkwardness of crutch walking with the hip and knee flexed.

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We have found that our cases could be classified into three groups (Table 1), depending upon the amount and type of concomitant medical disability existing as observed during their first

nonia have had pulmonary emboli from silent thromboses in the legs. It is important to realize that in the aged the manifestations of peripheral venous thrombosis and pulmonary embolization may be minimal and may be unrecognized unless sought for quite diligently.

Pulmonary Factors

Although failure of the cardiovascular system predominated as a cause of death, pulmonary complications were of importance (Table 4). Just as the vascular system becomes inelastic so also does the thoracic cage. The costal cartilages become calcified, and changes occur in the intervertebral disks of the thoracic spine, with ensuing deformities that contribute to the rigidity of the chest wall and lead to emphysema. The net results are poor respiratory mechanics, with improper drainage of the bronchial tree and thus a predisposition to pneumonia and atelectasis. Hence one must expect and try to prevent the occurrence of these complications. An expectorant such as potassium iodide may be used to thin out the bronchial secretions and prevent obstruction of bronchi with tenacious plugs of mucus. Deep breathing should be encouraged, and as much painless motion as possible in traction should be instituted. Exposure of the patient to upper respiratory infection should be scrupulously avoided. The use of penicillin both before and after operation has been of tremendous help in the prevention and treatment of lung infection.

Renal Factors

Renal factors deserve special attention in the elderly age group. Shock¹⁰ has shown in a study of elderly men that inulin clearance, a measure of glomerular filtration, is 60 per cent of normal, whereas Diodrast clearance which gives a more complete over-all picture of kidney function is decreased to 45 per cent of normal. The recent work of Trueta et al.¹¹ in demonstrating the renal shunt mechanism following fractures of extremities and other noxious stimuli makes it evident that trauma, with its concomitant shock may further decrease renal function to the point of serious decompensation. We have found that operation on a patient with an elevated or rising nonprotein nitrogen can have disastrous results. Of similar importance is the carbon dioxide combining power of the blood. One of the prime functions of the kidney is the regulation of the acid-base equilibrium of the body. It does this by a process of selective retention or excretion of various salts. An early manifestation of impaired function is often a loss of this fine discriminatory power. As a result there is a retention in the body of sulfates and phosphates at the same time that there is a loss of fixed base. This can lead to a rather severe acidosis which must be corrected prior to operation. If the nonprotein nitrogen is high or the carbon dioxide low

the condition is corrected preoperatively by the use of fluids, sodium lactate or bicarbonate and saline solution as indicated. If there is no chemical improvement or still further deterioration, operation should not be performed.

Renal-tract infection was seen in 10 of the 72 patients operated on either before or after surgery. It is important to maintain an adequate urine flow both in the prevention and in the treatment of this condition. In men urinary retention secondary to prostatic obstruction must be avoided, and constant drainage should be instituted whenever there are signs and symptoms of such a difficulty.

Complete studies on water and electrolyte balance have been presented by Maddock and Coller.^{12, 13} Sufficient fluid should be administered either by mouth or parenterally to maintain a urine output of 1000 to 1500 cc daily.

Diabetes Mellitus

There were 7 diabetic patients in the group. Of these 3 died. As a rule the elderly patient with diabetes of long standing presents a hazardous problem to both the surgeon and the internist. McKittrick¹⁴ has pointed out the necessity of more deliberate and careful preparation for operation on patients with diabetes. The 3 fatal cases were never well controlled, and the patients showed elevated blood sugars and continually lost large amounts of sugar in the urine. In 2 cases gangrene of the involved limb occurred and all 3 patients succumbed to overwhelming infection.

SUMMARY

A study of 100 patients over the age of seventy admitted to the Boston City Hospital with hip fractures revealed a significant number with pre-existing medical disabilities. A grouping of the cases according to type and severity of such disabilities and the response to medical therapy is presented. Group I comprised good surgical risks, Group II fair risks, and Group III patients on whom operation was contraindicated. The effect on the mortality rate of degenerative diseases in the cardiovascular, pulmonary and renal systems and the management of these diseases are discussed.

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underlying disease involving the cardiovascular system

In senescence degenerative changes take place throughout the body, leaving the various organ systems prone to breakdown at periods of stress and strain. Special attention should be given to symptoms referable to the cardiovascular, renal and pulmonary systems. Evaluation of cardiac cases depends a great deal on the history. This has been emphasized by Sprague,⁹ who points out that the history is of more importance than the stethoscope or electrocardiogram. Patients who have led normal, active lives with no symptoms of cardiac failure will offer no cardiac problem to the surgeon. On the other hand, patients whose activities have been restricted because of dyspnea or chest pain may be hazardous surgical risks. Dyspnea or cough may also indicate decreased pulmonary reserve. Renal disease may be manifested only by a history of polyuria or nocturia.

Physical examination. Mere inspection of the patient tells a great deal. Is the patient oriented? Disorientation is often the only manifestation of a cerebrovascular accident. Shock, which is present in all cases to a greater or lesser degree, may cause mild to severe changes. The patient who is oriented and who lies flat in bed in traction with no increase in respiratory rate will usually prove a good surgical risk.

An enlarged heart or the presence of murmurs in no way contraindicates surgery provided cardiac compensation is present. Cardiac rhythm is of special concern. Such arrhythmias as auricular fibrillation and premature ventricular systoles demand special attention and treatment.

Adequate examination of the lungs is difficult in these cases. The finding of rales is usually ominous. They may be due to shock or myocardial failure, or both, and may indicate hypostatic changes with infection. All these conditions require prompt adequate treatment.

Abdominal distention is occasionally seen after hip fracture. Causes such as incipient intestinal obstructions, uremia and cerebrovascular accident should be considered alongside post-traumatic ileus.

Laboratory data. The following studies are recommended: complete urinalysis, hemoglobin determination, red-cell count, white-cell count and differential, blood nonprotein nitrogen, fasting blood sugar and blood carbon dioxide combining power. An electrocardiogram is often indicated.

Evaluation of the patient as a surgical risk will frequently require twenty-four to forty-eight hours or longer. During this period shock is corrected, fluid balance is established, and the patient is placed in optimum condition to withstand operation. On the basis of the history, physical examination, laboratory studies and response to therapy the patient can be classified in one of the three groups proposed. Only patients in Group III should be re-

fused operation. If a patient is becoming worse under adequate medical management in traction, we do not believe that operation will in any way alter the course for the better. On the contrary, it will undoubtedly hasten death.

Cardiovascular Factors

The incidence of cardiovascular disease, of either the hypertensive or the arteriosclerotic type, is notably high in elderly patients. Their cardiac reserve is low, and they are easily thrown into congestive failure or shock by the altered circulatory dynamics following the trauma of hip fracture. No operation should be attempted on such patients until the cardiac failure has been corrected. Once this has been accomplished, no type of heart disease except recent myocardial infarction is a contraindication to hip nailing.

The routine use of digitalis in patients who are not in failure should be avoided, since it decreases cardiac output and increases the irritability of the myocardium and hence predisposes to the development of ventricular tachycardia or fibrillation. If there is any evidence of ventricular irritability, such as ventricular extrasystoles, the patient should be given 0.2 to 0.3 gm (3 to 5 gr) of quinidine every four hours. This drug is efficacious in preventing fatal cardiac arrhythmias that might develop during operation.

The vascular degenerative changes in the aged predispose to shock as a result of trauma. The widespread arteriosclerosis — and, therefore, the diminished elasticity and adaptability of the vascular system — does not permit the compensatory changes seen in the younger age group. Because of this, shock must be treated as early and as adequately as possible. This lowered capacity of the vascular system for adaptation should be kept in mind when fluids are administered intravenously, for a sudden increase in circulatory volume in these patients may be fatal.

The danger of arterial thrombosis is ever present. Although the occurrence of massive myocardial infarction is not common in the aged, there may be extensive small thromboses in branches of the main coronary arteries, and in spite of lack of chest pain and electrocardiographic changes, the patient may die of coronary-artery insufficiency. Thrombosis of arteries in the brain may be accompanied by no peripheral neurologic signs, the only manifestation of this catastrophe being a change in character or sensorium, abdominal distention or, worse, the development of a frank psychosis. Shock by slowing of the blood flow enhances the possibility of thrombosis in this age group.

Eleven of the patients operated on showed signs and symptoms of thrombophlebitis or phlebothrombosis. In these cases pulmonary emboli developed in 2, who died. This is a rather low figure, and it is quite possible that patients believed to have pneu-

monia have had pulmonary emboli from silent thromboses in the legs. It is important to realize that in the aged the manifestations of peripheral venous thrombosis and pulmonary embolization may be minimal and may be unrecognized unless sought for quite diligently.

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Although failure of the cardiovascular system predominated as a cause of death, pulmonary complications were of importance (Table 4). Just as the vascular system becomes inelastic, so also does the thoracic cage. The costal cartilages become calcified, and changes occur in the intervertebral disks of the thoracic spine, with ensuing deformities that contribute to the rigidity of the chest wall and lead to emphysema. The net results are poor respiratory mechanics, with improper drainage of the bronchial tree and thus a predisposition to pneumonia and atelectasis. Hence one must expect and try to prevent the occurrence of these complications. An expectorant such as potassium iodide may be used to thin out the bronchial secretions and prevent obstruction of bronchi with tenacious plugs of mucus. Deep breathing should be encouraged, and as much painless motion as possible in traction should be instituted. Exposure of the patient to upper respiratory infection should be scrupulously avoided. The use of penicillin both before and after operation has been of tremendous help in the prevention and treatment of lung infection.

Renal Factors

Renal factors deserve special attention in the elderly age group. Shock¹⁰ has shown in a study of elderly men that inulin clearance, a measure of glomerular filtration, is 60 per cent of normal, whereas Diodrast clearance, which gives a more complete over-all picture of kidney function, is decreased to 45 per cent of normal. The recent work of Trueta et al.¹¹ in demonstrating the renal shunt mechanism following fractures of extremities and other noxious stimuli makes it evident that trauma, with its concomitant shock, may further decrease renal function to the point of serious decompensation. We have found that operation on a patient with an elevated or rising nonprotein nitrogen can have disastrous results. Of similar importance is the carbon dioxide combining power of the blood. One of the prime functions of the kidney is the regulation of the acid-base equilibrium of the body. It does this by a process of selective retention or excretion of various salts. An early manifestation of impaired function is often a loss of this fine discriminatory power. As a result there is a retention in the body of sulfates and phosphates at the same time that there is a loss of fixed base. This can lead to a rather severe acidosis which must be corrected prior to operation. If the nonprotein nitrogen is high or the carbon dioxide low

the condition is corrected preoperatively by the use of fluids, sodium lactate or bicarbonate and saline solution as indicated. If there is no chemical improvement or still further deterioration, operation should not be performed.

Renal-tract infection was seen in 10 of the 72 patients operated on either before or after surgery. It is important to maintain an adequate urine flow both in the prevention and in the treatment of this condition. In men urinary retention secondary to prostatic obstruction must be avoided and constant drainage should be instituted whenever there are signs and symptoms of such a difficulty.

Complete studies on water and electrolyte balance have been presented by Maddock and Coller.^{12, 13} Sufficient fluid should be administered either by mouth or parenterally to maintain a urine output of 1000 to 1500 cc daily.

Diabetes Mellitus

There were 7 diabetic patients in the group. Of these 3 died. As a rule the elderly patient with diabetes of long standing presents a hazardous problem to both the surgeon and the internist. McKittrick¹⁴ has pointed out the necessity of more deliberate and careful preparation for operation on patients with diabetes. The 3 fatal cases were never well controlled, and the patients showed elevated blood sugars and continually lost large amounts of sugar in the urine. In 2 cases gangrene of the involved limb occurred and all 3 patients succumbed to overwhelming infection.

SUMMARY

A study of 100 patients over the age of seventy admitted to the Boston City Hospital with hip fractures revealed a significant number with pre-existing medical disabilities. A grouping of the cases according to type and severity of such disabilities and the response to medical therapy is presented. Group I comprised good surgical risks, Group II fair risks, and Group III patients on whom operation was contraindicated. The effect on the mortality rate of degenerative diseases in the cardiovascular, pulmonary and renal systems and the management of these diseases are discussed.

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ACUTE HERPETIC GINGIVOSTOMATITIS IN THE ADULT*

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PHILADELPHIA

THE majority of people, about 70 per cent, experience their first infection with the herpes simplex virus in infancy or early childhood. This infection is usually inapparent, and can therefore only be recognized as having occurred by the presence of circulating antibodies.¹ However, in about 1 per cent of all infections, the first attack of the virus can give rise to a serious or even fatal disease. These primary infections, of which the commonest is the clinical entity known as acute herpetic gingivostomatitis,²⁻⁶ are well recognized in childhood because they commonly occur in this age group. In adult life, however, these clinical manifestations, on the basis of the figures just quoted, rarely occur and therefore are liable to go unrecognized as herpetic infections. The common adult manifestation of infection is recurrent herpes labialis or "fever blisters." These recurrent attacks are usually accepted as being due to a reactivation, by non-specific stimuli, of the herpes virus that has lain latent in the tissues of the host since recovery from the primary infection, whether clinical or inapparent.

In view of these facts, it seems worth while to record the clinical picture of primary herpetic infection that occurred in 3 adult patients.

Youmans,⁷ in 1932, reported the first case in an adult in which the virus was isolated. Long⁸ described 3 cases with the isolation of the virus from two. Scott, Steigman and Convey⁹ observed a primary infection in a mother whose children were being treated for the same disease, in addition to isolating the virus, the authors demonstrated the development of neutralizing antibodies during convalescence. Scott¹⁰ discussed another case in a soldier in England from whom the virus was isolated, and the development of antibodies was demonstrated during convalescence. Ziskin and Holden¹¹ reported 8 cases of acute herpetic gingivostomatitis

in adults, and Florman and Trader¹² a case in an adult. In all these cases the clinical impression was corroborated by laboratory findings.

CASE REPORTS

CASE 1. A 21-year-old secretary was admitted to the Hospital of the University of Pennsylvania on December 3, 1947, complaining of sore mouth and fever. Her illness had begun 2 days previously, when she had discovered, on brushing her teeth, that the gums were extremely painful. She felt a little nauseated. For the next 2 days she felt chilly and feverish, and her gums became progressively worse. A slight headache developed, but there was no stiffness of the neck.

The patient had never previously had a cold sore or "canker sores." Her mother had typical herpes labialis at the onset of the patient's illness.

Since the patient was later found to have infectious mononucleosis, in addition to the herpes simplex infection, some further details about two febrile illnesses that occurred in the month preceding the onset of the present illness are presented. On November 1 a running nose, sore throat, and backache developed, and the patient was sick, with a fever, for 4 days. Her temperature reached a maximum of 102°F. She recovered and returned to work until November 14, when a sore throat and fever of 4 days' duration occurred, the temperature rose to a maximum of 102°F. During this illness, she was under the care of her family physician, who made a diagnosis of acute tonsillitis and treated her with sulfadiazine. When seen by one of us (A. M. R.) in consultation on November 17, she had a temperature of 100°F, and was feeling much better than she had for the previous 2 days. Her pharynx was moderately inflamed, and both tonsils were enlarged and partially covered with a gray-white exudate. No blood counts or other laboratory studies were done at this time. She recovered from this illness and returned to work on November 24, working regularly until the day of admission.

Physical examination revealed that the breath was foul, the gums were swollen and inflamed, especially along the gingival margins, and bled easily on manipulation, inside the lower lip at the angle of the mouth were two aphthous ulcers, and many unruptured small blebs were scattered throughout the buccal mucosa. On the left buccal mucosa there was a white, desquamating patch, 1 cm. in diameter. The submaxillary and posterior cervical lymph nodes were enlarged and tender. No other lymph nodes were enlarged. The spleen was not palpable.

The temperature was 103.4°F.

Examination of the blood showed a hemoglobin of 81 per cent and a white-cell count of 6100, with 53 per cent neutrophils, 21 per cent monocytes, 24 per cent lymphocytes, 1 per cent eosinophils and 1 per cent basophils. No immature cells were seen. On December 6 an essentially similar count was obtained except that a few immature atypical lymphocytes were noted. Urinalysis on three occasions was negative. A gingival smear for Vincent's organisms taken on the day of admission was negative, and a throat culture revealed a normal flora. Blood drawn for heterophil-antibody tests on December 6 revealed a titer of 1:5096, which was reduced to 1:448 after absorption with guinea-pig antigen, and was completely absorbed by beef-cell antigen.

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The mouth lesions increased in severity, and on December 6, 51 distinct aphthous ulcers were counted on the uvula, tongue, buccal mucosa, gingiva and hard palate. They were equally distributed on both sides. Enlarged and tender submental lymph nodes were noted at this time. The temperature became normal on the 8th day of illness, and the patient was discharged to her home. She reported on December 11 that she had only three unhealed lesions. When she was seen on December 15 no lymphadenopathy was present, and the oral mucous membranes were normal except for a slight redness along the gingival margins, which had disappeared by December 29.

In February, 1948, the patient complained of painful, bleeding gums for a week. In March an aphthous ulcer appeared on the buccal mucosa, but the virus of herpes simplex could not be isolated at this time, and a biopsy of the ulcer showed no typical inclusion bodies. Since then the patient has had no trouble with her mouth.

The diagnosis of herpetic stomatitis was confirmed by three methods: isolation of the virus of herpes simplex from the oral lesions, biopsy of one of the mouth lesions, and demonstration of neutralizing antibodies in the convalescent serum that were absent in the serum taken at the onset of the disease.

On December 4, 1947, saliva was collected and, after treatment with penicillin and streptomycin, was inoculated onto the chorioallantoic membrane of embryonated hens' eggs. Subsequent examination of the membrane showed numerous plaques similar to those produced by the virus of herpes simplex. The virus was propagated serially in eggs, and was specifically neutralized by rabbit antiserum for the HF strain of herpes simplex virus. Biopsy of one of the ulcers of the patient's mouth was taken on December 4, 1947. In the microscopical section stained with hematoxylin and eosin, balloon-

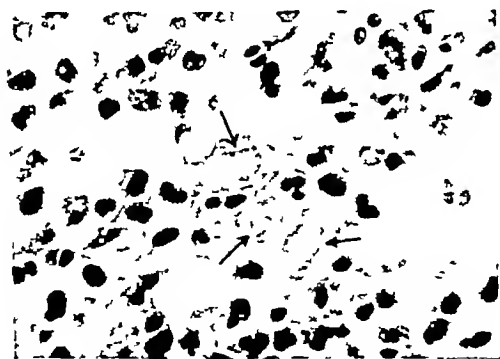


FIGURE 1 Biopsy of Aphthous Ulcer of the Buccal Mucosa in Case 1

Three swollen epithelial cells containing herpetic inclusion bodies that completely fill the nucleus are surrounded by an inflammatory exudate (hematoxylin and eosin stain $\times 300$)

ing cells containing intranuclear inclusion bodies typical of herpes simplex infection were seen in the epidermis (Fig 1). Neutralization tests were carried out on the egg membranes with the HF strain of herpes-simplex virus and the patient's acute and convalescent serums. No neutralizing antibodies were present in the serum drawn on December 4, whereas the 1:16 dilution of serum drawn on December 15 completely neutralized the standard strain of herpes simplex virus.

CASE 2 E. C., a 34-year-old housewife, was seen at home on September 20, 1947, with the chief complaint of "sore mouth," headache, backache and malaise of 1 day's duration. She dated the onset of the sore mouth and gums from the previous day, when she had massaged her teeth and gums vigorously. She had never had a cold sore in her life, although her husband had frequent cold sores and was recovering from a recent attack at the time.

Physical examination showed the anterior cervical lymph nodes to be swollen and tender, the gums were slightly

swollen and red, especially along the gingival margin. On the following day the temperature was 100°F, the gums were more swollen and more inflamed, and several aphthous ulcers were seen inside the lower lip, on the tongue and on the gingiva. Several grouped vesicles were seen on the lips at the left angle of the mouth. The malaise, fever and sore mouth persisted for 1 week. On September 30, a few healing ulcers were still visible on the gingiva and lips, although there was no subjective pain at this time.

The temperature by mouth was 99.1°F.

Gingival smears were made for Vincent's organisms on September 21, 26 and 30, all were negative. A culture of the gingiva on September 21 revealed no abnormal bacteria. From saliva collected on September 23, herpes-simplex virus was isolated in chick embryos. Serums taken during the acute and convalescent stage of the disease showed a rise in titer of neutralizing antibodies for herpes simplex from 0 to 1:16.

CASE 3 A 1st-year medical student noted the onset of his illness on April 22, 1948, when the submental and submaxillary lymph nodes became tender and swollen. On the following day, the gums were sore, and he began to feel chilly and feverish intermittently. For the next 4 days the soreness



FIGURE 2 Appearance of the Mouth in Case 3 on the Sixth Day of the Disease, Showing Five Aphthous Ulcers of the Mucous Membrane and One of the Iermilion Border

The gingivae are red and swollen

of the gums progressed and involved the cheeks, tongue and throat. He was admitted to the Student Health Service of the University of Pennsylvania with an oral temperature of 100°F and a pulse of 90.

Physical examination revealed a moderate bilateral cervical adenopathy, with ulcerations on the lips, buccal mucosa, tongue and tonsils (Fig 2). A palpable lymph node was felt in the left axilla. No other nodes were enlarged. The spleen was not felt.

The urine was normal. Examination of the blood disclosed a white-cell count of 8000, with 71 per cent neutrophils, 26 per cent lymphocytes and 3 per cent monocytes. The temperature rose to a maximum of 100.6°F, and then gradually subsided over the next 4 days, reaching normal on the 9th day of the disease. The mouth lesions continued to progress and became worse until the 8th day of the disease. From then on, the healing was quite rapid. On April 28 a heterophil-antibody test was negative, as was a serologic test for syphilis. Neutralizing antibodies against the herpes-simplex virus were absent from the serum taken on the 7th day of the disease, but present in serum drawn 2 weeks later.

DISCUSSION

The clinical features of the 3 cases presented are similar to those previously reported in both children

and adults. No patient gave a history of previous fever blisters or canker sores, and in 2 cases recent contact with a person who had a cold sore suggested a likely source of infection. The chief complaint of the 3 patients was sore mouth, fever and malaise. Inspection of the oral cavity revealed in some cases vesicular lesions, but chiefly many small, shallow discrete ulcers measuring 1 to 5 mm in diameter. The gingivae were acutely inflamed along the margin. Ulcerations were frequently present on the alveolar and palatal gingivae. The regional lymph nodes were uniformly enlarged. The temperature varied from 100 to 103°F by mouth, returning to normal during the course of a week. New lesions kept appearing in the mouth during the first few days, and remained painful throughout the first week. Healing gradually occurred during the second week, without scarring.

In the 2 cases so examined, the total white-cell count was not elevated. Except in the patient who was recovering from infectious mononucleosis, the differential counts were normal. In the 3 cases reported by Long,⁸ the white-cell and differential counts were within normal limits.

The diagnosis of infection with herpes-simplex virus was confirmed in each case by the demonstration of the development of specific neutralizing antibodies during convalescence. In 2 cases the herpes-simplex virus was recovered from saliva, and typical inclusion bodies were seen in sections of biopsy material in 1.

The sudden onset of fever, sore mouth and regional adenopathy in a previously healthy adult immediately presents a problem of differential diagnosis. The diagnostic probabilities include Vincent's infection, or trench mouth, erythema multiforme, infectious mononucleosis, syphilis, agranulocytosis, acute leukemia, pemphigus vulgaris and diphtheria of the pharyngeal or tonsillar region.

A negative peridental smear for organisms of the Plaut-Vincent type is helpful, but a positive smear is of no value because these organisms are frequent in normal mouths, and more frequent in the presence of acute inflammation when pain prevents proper cleansing and oral hygiene. Burket¹³ and Ziskin and Holden¹¹ stress ulceration of the interdental papilla as the typical lesion of acute Vincent's infection, and in severe cases they describe ulcerations covered by a gray or yellow pseudomembrane on the palatal, buccal and labial mucosa. The fusospirochetal infection can be controlled by penicillin therapy, which does not shorten the course of the herpetic gingivostomatitis.

The treatment is symptomatic. The use of tetracaine hydrochloride 1 per cent (Pontocaine Hydrochloride) or p-amino-benzoyl-dibutyl-amino-propanol sulfate 2 per cent (Butyn Sulfate) locally before meals affords much comfort. The intense soreness of the gums makes brushing of the teeth impossible, so that irrigation of the mouth is essential.

We have used benzalkonium chloride 1-1000 (Zephiran) or cetylpyridinium chloride 1-4000 (Ceepryn) for that purpose. Penicillin should be used to control secondary infection by fusospirochetal organisms or pyogenic cocci.

Recurrent fever blisters are generally accepted to be manifestations of a recrudescence of a latent herpes-simplex virus, but there is no laboratory evidence that recurrent aphthous ulcers are caused by this virus. It is interesting to note that one of the patients did have a "canker sore" for the first time in her life after recovery from the primary infection. However, no herpes virus was recovered, nor were the inclusion bodies seen in a biopsy specimen of this lesion.

Levine et al.¹⁴ reported, as probably herpetic in origin, an epidemic of vesicular pharyngitis and stomatitis that involved almost 50 per cent of 230 people in a summer camp. Recent knowledge of the epidemiology and clinical manifestations of herpes indicates that this epidemic was not due to infection with the virus of herpes simplex for the following reasons: most people over three to five years of age have already contracted a primary infection and are immune to reinfection from without, vesicles, rarely observed in herpetic gingivostomatitis, were "present in all the epidemic cases", the ulcers were "grayish yellow," in contrast to the whitish ulcers of herpes, and some of the most consistent findings in herpes infection—marginal gingivitis, pain and regional lymphadenopathy—were minimal or present in less than half the epidemic cases. We have observed a small epidemic of the syndrome described by Levine et al. and were unable to isolate a virus or to demonstrate a rise in neutralizing antibodies for herpes simplex during convalescence.

SUMMARY

Three cases of acute herpetic gingivostomatitis in adults are reported. The clinical picture is described, and its similarity to the disease in infants is noted—namely, an acute, febrile illness with malaise, chilliness, multiple aphthous ulcers of the mouth and pharynx, marginal gingivitis and regional-lymph-node enlargement.

The methods by which a positive diagnosis may be established in the laboratory are illustrated: isolation of the virus, demonstration of typical inclusion bodies in a biopsy specimen, and the appearance of specific neutralizing antibodies in the serum during convalescence.

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RADIATION EXPOSURES FROM THE USE OF SHOE-FITTING FLUOROSCOPES

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IT IS now common practice in many shoe stores and shoe departments of department stores to supplement usual shoe-fitting methods by the use of fluoroscopes known as x-ray shoe fitters. Because this technic has spread rapidly throughout the United States, particularly in stores specializing in children's shoes, it is desirable to know precisely the exposures to irradiation received by customers as well as by clerks and other persons in the area of x-ray shoe-fitting units.

For this reason a series of studies was undertaken for the purpose of measuring foot dosage, leakage through the walls of the cabinet and scattering from the opening in which the customer places his feet. The data obtained form the basis of this report.

EQUIPMENT

The unit consists essentially of a 50-kv x-ray tube operating at 3 to 8 milliamperes through a 1-mm aluminum filter, housed in a case lined with lead or steel and containing a fluorescent screen. The focal spot to skin distance is 7.5 to 20 cm. The unit is equipped with an opening for the customer's feet and three viewing openings through which the customer, clerk and one other person can observe the screen. A push-button automatic timer, which can be set for any predetermined time, is included on most installations. In actual use exposure times have been found to vary from five to forty-five seconds although twenty seconds appears to be the most popular setting. *Repeated exposures can be made by releasing and pushing of the button.* More recent models are equipped with three separate switches providing three different intensities — one for men, one for women and one for children.

FOOT DOSAGE

The amount of radiation delivered to the feet of the customer is a quantitative matter related to tube output, focal skin distances and time of exposure. A large series of measurements (on 12 units) using a Victoreen r-meter placed inside a shoe

showed wide variations in the quantity of radiation delivered to the feet.

Figure 1 shows dosage curves for several typical units. Total exposure values were determined for a series of time settings on each shoe-fitter. By the plotting of total r against time the results establish a straight line from which dosage rate can

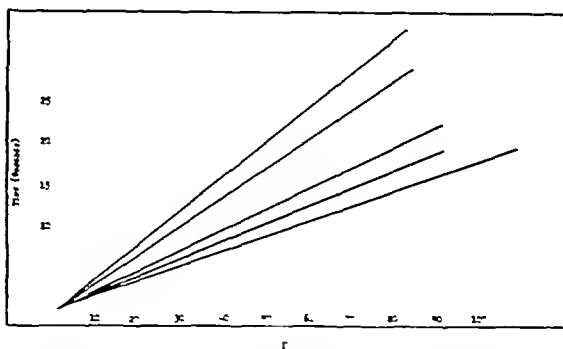


FIGURE 1 Foot Dosage in Shoe-Fitting Fluoroscope
The timer is normally set for twenty to twenty-two seconds

be derived. All installations tested fall within the range of the curves shown — that is from 0.5 to 5.8 r per second. By multiplying total exposure time and dosage rate, one can determine the total foot dose per exposure. Thus for a twenty-second exposure (that most commonly used) doses ranging from 10 to 116 r could be delivered to the feet of a customer. Repeated fittings increase the exposure in proportion to time.

SCATTERED RADIATION

This is defined in the American Standards Association Code (Paragraph 3-2.1.3)¹ as "radiation which during passage through a substance has been deviated in direction and also may have been modified by an increase in wavelength." The foot opening in shoe-fitting units is the most important source of radiation of this type. After passing

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through the aluminum filter and the customer's feet it escapes from the cabinet through the opening. In most installations this amounts to more than 100 milliroentgens (mr) per hour at 10 feet from the unit and 15 mr per hour at 25 feet. The zone of scattered radiation in excess of 15 mr per hour covers an area of about 90° from the foot opening out into the room.

Figure 2 shows a typical setup in a shoe store. It should be noted that at many of the seats where customers are given preliminary fittings, an area in which clerks may be working, a total daily dose

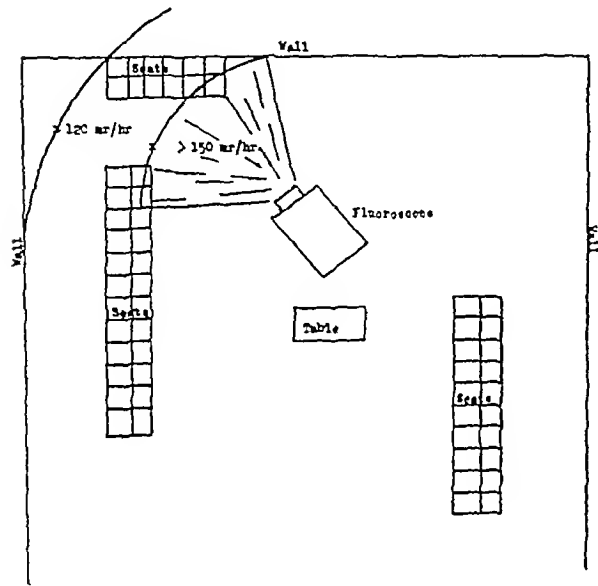


FIGURE 2 Distribution of Scattered Radiation from Shoe-Fitting Fluoroscope

could be received in one hour of operation by anyone in the area.

CABINET-WALL LEAKAGE

Measurements of leakage directly through the walls of the cabinets showed wide differences between units. These differences varied with manufacturer, age and condition of the equipment and condition of the x-ray tube.

Values were obtained using two rate meters — a Zeus survey meter with a range of 0 to 2500 mr per hour and a Victoreen radiation meter having a range of 0 to 20 mr per minute (0 to 120 mr per hour). Readings were taken at the sides, front, back and in the zone where viewing is done. The front of the machine is the side on which the control buttons are located, the back is where the customer stands. It should be noted that values found on the back are influenced by scattering from the opening where the feet are placed.

It can be seen from Table 1 that there is some leakage directly through the walls of the cabinets.

The figures represent the dosage rates received by persons adjacent to the cabinet. They can be evaluated in terms of the permissible daily dose of 100 milliroentgens (12 mr per hour) as established by the American Standards Association.¹ The length of time for which a person can be in close proximity to one of these units can be determined by comparison of the leakage (rate) with the permissible

TABLE 1 Leakage through Walls of Shoe-Fitting Fluoroscope*

SITE OF LEAKAGE	NO. OF UNITS	AMOUNT OF LEAKAGE		
		BOTTOM mr/hr	MIDDLE mr/hr	TOP mr/hr
Front	12	3 to 6	12 to 48	12 to 36
Sides	12	7 to 60	12 to 36	8 to 24
Back	12	200	30 to 100	6 to 54
Viewing position	12	Values range from 0 to 24 mr per hr		

*Taken at the walls

daily dose. The leakage must be measured for each unit.

CONTROL OF EXPOSURE

There are many steps that should always be taken in the use of this equipment to minimize exposures to customers and clerks. Each unit must be treated as an individual problem.

Foot dosage. The control of foot dosage depends on four factors: the output of the tube, thickness and condition of filters, distance, time of exposure and number of exposures. The control of the first two rests with the manufacturer, and that of the last two with the store.

The American Standards Association¹ and the New York City Health Department² have specified that "The maximum permissible dose per exposure shall not exceed 2 roentgens." New York City requires further that "There shall not be more than 3 exposures in one day and not more than a total of 12 exposures in one year." The only attempt to enforce this provision is a requirement for posting of signs on the machines stating "REPEATED EXPOSURES TO X-RAYS MAY BE HARMFUL. FLUOROSCOPIC EXAMINATIONS FOR SHOE FITTING SHOULD BE LIMITED TO NO MORE THAN 12 IN ONE YEAR." These signs should measure at least 7½ inches by 4½ inches and should be posted conspicuously.

More recent proposals by the Bureau of Industrial Hygiene, Detroit Department of Health,³ require that maximum intensity in the beam shall not exceed 12 mr per minute and that maximum time of exposure shall not exceed five seconds. The same dose limit is being recommended by the Division of Occupational Hygiene of the Massachusetts Department of Labor and Industries. Based on this figure, suggested warning signs state that the

limit for each customer shall be 3 x-ray shoe fittings per day and no more than 12 fittings per year.

These figures indicate the exposure levels now being established by municipal and state authorities in their regulations to control the use of shoe-fitting fluoroscopes.

Scattered radiation and wall leakage. Leakage through the walls of the equipment can be controlled only by the manufacturers, since it depends on shielding in the cabinet and the tube output.

Control of scattered radiation is the responsibility of the user because the controlling factor is the position of the unit with respect to occupied areas.

The New York City Sanitary Code (Section 107a) specifies under Regulation 2 that — "The equipment shall be so constructed that the dosage rate in any region which may be occupied by operators and attendants does not exceed 12.5 milliroentgens per hour." It is obvious from the data shown in

the section on scattered radiation that the back (customer's) side of these units should never be directed toward occupied areas within a radius of 25 feet.

SUMMARY

Measurements on shoe-fitting fluoroscopes in use show that foot dosages may range from 0.5 to 5.8 r per second (time of exposure five to forty-five seconds), that wall leakage may range from 3 to 60 mr per hour and that scattered radiation amounts to more than 100 mr per hour at distances up to 10 feet from the unit.

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POTENTIAL DANGERS IN THE UNCONTROLLED USE OF SHOE-FITTING FLUOROSCOPES*

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BOSTON

THREE types of radiation injuries may result from the uncontrolled use of low-voltage x-ray machines in shoe stores in the manner described by Dr. Williams in the preceding article. The most likely injuries are interference with normal foot development of children who are fluoroscoped repeatedly when being fitted with new shoes, acute radiation burns of the customer's feet resulting in late permanent skin damage, chronic radiation injury of the blood-forming tissue of store employees who work with improperly shielded x-ray machines. Little is known concerning possible effects of this type of radiation on the sex glands. Some of the unusual features of these injuries will be discussed, and the possibility of their being caused by existing shoe-fitting fluoroscopes will be considered.

POSSIBLE TYPES OF INJURY

Interference with Foot Development

Growing bone, in contrast to adult bone and hyaline cartilage, is easily damaged by exposure to x-rays. This is due to the radiosensitivity of the epiphyseal cartilage. Damage to this tissue is manifested by reduction in the rate of bone growth and by premature closure of the epiphyseal junction. Experimental studies in animals of the action of x-rays on the epiphyses bring out certain

facts that are related to the present problem. It has been shown that the younger the animal, the greater the effect on bone growth of a given dose of x-rays.¹ In addition, stunting of bone growth in animals can be produced by less than half the dose of 200 kv that will cause erythema of the overlying skin. It has also been demonstrated that fractionation of the dose and prolongation of the intervals between exposure lessen the effect of the radiation on epiphyseal cartilage as well as on other tissue.²

Clinical reports describe cases of cessation of bone development in children who receive radiation therapy for lesions in the region of the epiphyses.³ Therapeutic use has been made of the growth-stunting property of x-rays to minimize inequality in limb length caused by osteomyelitis or other types of bone disease.³ The minimal stunting dose of x-rays has been stated to be a quarter of the erythema dose for infants and half the erythema dose in older children.⁴ If this statement is correct, a few hundred of moderately hard x-rays administered in a single exposure will cause a disturbance in foot development in young children.

Aside from the fact that the epiphyses are extremely radiosensitive, the most important lesson to be learned from clinical experience and from animal experimentation is that abnormal bone development can be produced insidiously in the absence of skin damage or other external evidence of radiation injury. Before the other types of radiation damage are considered it should be stated

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that the dosages mentioned in the literature usually refer to more penetrating radiation than that delivered by shoe-fitting fluoroscopes. Consequently, the dose of soft x-rays necessary to damage epiphyseal tissue lying 1 or 2 cm below the skin surface would be more nearly equal to the erythema dose.

Radiation Burns of the Skin

The acute and chronic types of x-ray reactions of the skin are so well known that they need not be described. Innumerable cases of such injuries have been reported in the last fifty years, and yet the data concerning the radiation dosages that cause skin damage, except for that delivered as an acute exposure, are almost nonexistent. At least 600 to 1000 r of soft x-rays given within a day or two would be required to produce a serious skin reaction. If the radiation dosage were fractionated, higher total doses would be necessary to produce comparable skin damage. Little is known of the radiation dosages that cause chronic skin damage. It has been suggested that repeated exposure of the hands to $\frac{1}{4}$ r of gamma rays per week over a period of many years may produce injury.⁵ There is no published information bearing on the maximum radiation dosage that can be administered to the skin with safety at the intervals at which children are likely to be fitted for new shoes (two to four months).

Chronic Radiation Damage of the Blood-Forming Tissues of Store Employees

The hazards involved in repeated exposure of the body to soft x-rays are similar to those encountered in any hospital or physics laboratory that uses x-ray machines or radioactive material. The dangers to blood-forming tissues of chronic overexposure of the body to x-rays are familiar to everyone. Recent experiments illustrate how irradiation with small daily doses of x-rays reduces the life span of animals.⁶ The maximum permissible dose of radiation to which persons can be safely exposed throughout their working lives has been considered for many years to be 0.1 r per day. Within the past few months, however, the Advisory Committee on X-Rays and Radium⁷ has reconsidered this dose and recommended that it be lowered to 0.3 r per week.

DISCUSSION

Consideration of the radiation dosages measured by Dr. Williams, in the light of the biologic information presented, suggests that injury to either the epiphyseal cartilage or the skin is unlikely after a single exposure to the shoe-fitting fluoroscope except under the most undesirable conditions. Several fittings within a day or two may conceivably lead to epiphyseal damage in children or to skin damage in children or adults. Repeated fluoroscopy of the foot by improperly regulated machines

from early childhood to the age of normal closure of the epiphyses (eighteen to twenty years) could result in foot deformities and even in permanent skin damage.

To prevent injury to customers and employees, it is obvious that the use of x-ray machines in shoe stores must be controlled. Proper shielding of the fluoroscope to minimize radiation leakage, education of the users and store officials about the dangers involved in misuse of the machines and reduction of the foot dosage per viewing must be accomplished. Shielding of a low-voltage fluoroscope is a relatively simple matter. Conspicuous warning signs on each machine can help to educate the public to the dangers of too frequent use of fluoroscopy, restriction of the use of x-ray machines to qualified personnel will reduce the possibility of accidental overexposure. Reduction of the foot dosage per exposure can be accomplished by lowering of the tube output, by adequate filtration and by limitation of the exposure by automatic timing devices. Since the maximum amount of radiation that the foot can tolerate at intervals of several months is not known, it seems advisable to reduce the foot dosage to the minimum that is compatible with satisfactory use of the fluoroscope. As Dr. Williams has indicated, the foot can be visualized adequately in a fluoroscope that delivers 1 r in a five-second exposure. Therefore, the newly issued recommendations of the Massachusetts Department of Hygiene (1 r per viewing, three exposures per day and twelve exposures per year) seem to be preferable to the higher dosages permitted by the American Standards Association and the New York City Health Department regulations quoted in the preceding article.

SUMMARY

It may be said that the type of radiation injury most likely to result from the unsupervised use of low-voltage fluoroscopes in shoe stores is the malformation of the feet of growing children. Such deformities may occur in the absence of x-ray reactions of the skin. Skin damage of the feet of customers and injury of the blood-forming tissues of store employees are possible consequences of the misuses of the shoe-fitting fluoroscopes. These dangers can be controlled by proper regulation of the use of the machines.

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MEDICAL PROGRESS

GASTROINTESTINAL ALLERGY (Concluded)*

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BOSTON

LABORATORY TESTS

In patients suspected of gastrointestinal allergy demonstration of the allergic response has at times been sought by radiologic studies. For the most part, the patient has first been examined by means of a barium-in-water meal, followed in a few days by a similar examination, a suspected food being given with or a few hours after the barium suspension. In patients so examined, whether adults or children, the most common finding at the second test was delayed gastric emptying, usually interpreted as indicating allergic pyloric spasm or edema.^{31 40 63 64} This interpretation, however, may be questioned on many counts. All foods, particularly those containing fats, may delay gastric evacuation. In normal children, the painstaking studies of Macy et al^{65 66} show that a barium-water meal leaves the stomach in one and eight-tenths to two and eight-tenths (average one and nine-tenths) hours, but that a barium-milk suspension requires one and five-tenths to four and five-tenths (average three and one-tenth) hours to leave the stomach. An adult stomach may evacuate all of a water meal within an hour but only 20 per cent of a milk meal of similar size.⁶⁷

Against this background, the effects of an allegedly allergenic food cannot be differentiated easily from the normal effect of food on gastric emptying. In fact, those who appreciate that foods delay gastric evacuation postulate abnormal mechanisms only if this expected response does not occur. Thus Macy et al⁶⁵ observed that the milk meal emptied more rapidly than the water meal in one case. To explain this phenomenon, they invoked allergy. The same authors,⁶⁶ however, caution that "many factors are interrelated in the determination of the response of the alimentary canal: the method of measurement, the size of the meal ingested, its temperature, consistency, and content, the nutritional state of the individual and the emotional and environmental condition to which the individual is subject at the time."

If gastric evacuation is delayed the interpretation of pylorospasm is made, as pointed out by Fries and Mogil⁶⁸ only by inference. Gastric evacuation is controlled by a number of factors. Of

primary importance is gastric and duodenal motility rather than isolated spasm of the pyloric sphincter.⁶⁸ Hence, to explain retarded emptying of the stomach on this basis is usually incorrect.

The ingestion of an allergen is also credited with changing small-intestinal motility as demonstrated by a barium meal. The changes seen are irregular transport, abnormal luminal caliber and enlarged mucosal folds, the entire picture frequently resembling the so-called "deficiency pattern."⁶⁹ This pattern, however is not at all specific,⁷⁰ and adequate control studies are not available to exclude the likelihood that the observed changes were caused by food given irrespective of the presence of allergy. The ingestion of milk certainly may produce definite changes, either relaxation of intestinal loops or hypertonic segmentation spasm and rapid transport. Whether this so-called "milk-reaction" is allergic in nature is discussed by Golden.⁶⁹ Although he states that "a diagnosis of intestinal allergy cannot be made on the basis of the roentgen examination at the present time," he believes that hypertonicity and rapid transit in the lower small bowel after the ingestion of milk or other foods suggests allergy. To support this contention, he presents a number of carefully documented cases which, if allergic, again illustrate the inconstant characteristics of gastrointestinal allergy. In one case, allergy of the small bowel is demonstrable by a barium-in-water meal, in another, the meal must contain the offending food, in a third the ingestion of one egg is without effect but a second induces disorder of motor function.

The difficulties of studying allergic reactions of the small intestine are shown in the objective and carefully evaluated work of Wing and Smith.⁷¹ Of 9 patients studied after exposure to a supposedly allergenic food, 7 showed some variation in small-bowel pattern but in only 3 was the change sufficient to exclude, in the authors' opinion a non-specific reaction, and 1 of these suffered from mild ulcerative colitis. The same authors observed no change in the intestinal pattern of sensitized guinea pigs when the antigen was fed. Intravenous injection of the antigen produced anaphylaxis but no significant effect on the radiologic appearance of the small intestine.

X-ray study of the colon exposed to allergens has been fragmentary. In 17 patients given allergen-containing barium enemas, Fries and Mogil⁶⁸ de-

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tected signs of irritability, such as spasms and local constrictions

In summary, radiologic study of the gastrointestinal tract occasionally reveals such marked derangements of appearance and motility after the ingestion of a food that a causal relation between the food and the observed reaction may be assumed, particularly if the x-ray findings are associated with symptoms. The problem is this: How can one be sure that the changes induced are allergic rather than nonspecific? A solution lies in more extensive use of control studies, adequate to exclude nonspecific effects. X-ray evidences of primary intestinal dysfunction are, as Weber⁷² states, "presumably valid when properly controlled. In no field of roentgenologic diagnosis is the exercise of critical judgment and objectivity more necessary, if unwarranted deductions and correlations are to be avoided," and, in referring to the barium enema, "In my opinion the evidence of abnormal physiologic change brought to light with its use is highly unreliable. I hesitate to attach abnormal physiologic significance, for example, to a contracted portion of the sigmoid colon, to a general increase or decrease in the caliber and length of the intestine."

Direct observation of the gastric mucosa by means of the gastroscope should reveal whether this tissue displays transient urticarial edema as may the mucous membranes of the naso-oropharynx. A number of case reports illustrating precisely such a reaction have been collected from the European literature by Schindler.⁷³ Typical is the case of Chevallier,⁷⁴ that of a bee-keeper who, when stung by a bee, fainted, developed generalized urticaria and exhibited symptoms suggesting pyloric obstruction. Gastroscoy performed during one of these episodes revealed transient edema of the antral mucosa. Although the number of such cases is not large and the patients apparently were not seen by Schindler himself, he accepts acute allergic urticaria of the stomach as a rare but definite entity. In this, he receives strong support from the excellent studies of Pollard and Stuart.⁷⁵ These workers used the gastroscope to examine 6 patients before and after ingestion of foods that seemed to produce upper gastrointestinal symptoms. In each case ingestion of the food was followed in thirty to sixty minutes by symptoms, accompanied by changes involving the lower third of the stomach: hyperemia, broadening of the rugal folds, boggy edema, diminution of peristalsis and a lumpy appearance of the mucosa. Seven patients (some with asthma but no gastrointestinal symptoms) were studied as controls. The ingestion of foods in these cases also produced mucosal hyperemia and edema but, in the opinion of the authors, to a much less degree than in the patients with symptoms. Gastrosopic observations tend to strengthen the impression that allergic reactions may occur in the stomach

Skin tests enjoy a varied reputation in the diagnosis of gastrointestinal allergy. The preparation of food extracts for skin testing is complicated by the tendency of certain substances to lose their allergenic activity very rapidly,²³ as well as by the occasional presence in foods of irritants that may produce skin reactions on some basis other than an allergic one. To these difficulties may be added the possibility²³⁻⁴¹ that the allergen in some foods is a product of digestion, and special procedures may then be required for the preparation of suitable extracts.

Most workers have been discouraged with attempts to apply skin tests to the diagnosis of gastrointestinal allergy. Positive skin reactions, though generally regarded as indicating allergic sensitivity of the skin to the substance injected, do not necessarily indicate similar sensitivity of the gastrointestinal tract, nor are negative reactions considered adequate evidence on which to exclude it. These views are based on the absence of correlation between the reaction observed in the skin and the occurrence of gastrointestinal symptoms on exposure of the patient to the substance from which the extract was made.

In attempting to assess the significance of skin reactions in gastrointestinal allergy, we are faced with a further difficulty, which appears to us, for the present at least, to be unsurmountable. As pointed out in this review, the criteria on which a diagnosis of gastrointestinal allergy is usually based leave a good deal to be desired. It is clearly impossible to arrive at a conclusion regarding the value of skin tests in the diagnosis of gastrointestinal allergy until this entity has become better defined.

Variations in the number of leukocytes, eosinophils or thrombocytes following the ingestion of foods have been presented as criteria for making the diagnosis of gastrointestinal allergy.^{29, 58, 64, 76-83} The best known of these tests is the leukopenic index, which was introduced in 1934 by Vaughan⁷⁶ as a means of detecting specific allergens that he believed were responsible for a variety of complaints, such as abdominal pain, urticaria, headache, neuritis, vertigo, asthma, colitis, eczema and indigestion. The usual manner of carrying out this test is as follows: two specimens for white-cell counts are drawn at ten-minute intervals in the fasting state, the test food is then eaten, and counts are done every fifteen minutes for an hour, and a final count is made at an hour and a half. A drop of 1000 cells per cubic millimeter below the mean of the two fasting counts is considered to signify hypersensitivity to the food ingested. The validity of this test is disputed,⁸⁴⁻⁸⁸ and its technic is open to criticism. Loveless et al.⁸⁴ showed that leukocytosis is not the normal response to the ingestion of foods, thus invalidating one of the premises upon which this test is based. Furthermore, postprandial leukopenia occurred with equal rarity

in both food-sensitive and nonsensitive subjects, and the incidence of this leukopenia was that which might result from the random variations that occur in the performance of successive blood counts. Loveless⁵⁴ also demonstrated that the development of asthma, hay fever and urticaria in a small group of ragweed-sensitive patients given ragweed extract subcutaneously was not associated with significant change in the leukocyte level. These findings were confirmed by Brown and Wadsworth,⁵⁵ who found no proof of the existence of either postprandial leukocytosis or an anaphylactic postprandial leukopenia. In spite of this evidence, this test continues to be employed as a means of diagnosing food allergy.⁷⁷⁻⁸² For this reason, it may be emphasized that in the usual technic of counting white cells, the error in duplicate samples may be as much as 20 per cent, and that the coefficient of variation is 10.7 per cent when the total count approximates 7000.⁵⁶ Consequently, the criterion of a reduction of 1000 cells per cubic millimeter that is used in the leukopenic index⁷⁶ would be met in about 1 out of 5 determinations on the basis of random variation alone. Spontaneous fluctuations in the number of circulating leukocytes further impair the significance of a 1000-cell change in the white-cell count.

Similar considerations apply to tests using a rise in eosinophils⁷⁵ or a fall in platelets⁵⁵⁻⁵⁸ as criteria for the diagnosis of an allergic gastrointestinal reaction to foods. Technical difficulties pertain particularly to the enumeration of thrombocytes. The technic of making eosinophil counts is usually not described in the papers employing this method. Hansen,⁵⁷ using a direct counting technic,⁵⁸ believed that a rise of 50 eosinophils per cubic millimeter after the ingestion of a food indicated hypersensitivity. As recent studies have amply demonstrated, however, the number of circulating eosinophils and white cells may be influenced by factors that are unrelated to allergy.⁵⁹

Since Walzer⁶⁰ and Hecht et al.⁶¹ suggest, on the basis of their experimental studies, that gastric acidity inhibits the gastrointestinal reaction to allergenic foods, the question arises whether patients with hypoacidity or anacidity are particularly susceptible to gastrointestinal food allergy. Individual case reports of patients believed to be suffering from such allergy mention gastric hypoacidity as a contributory factor,⁶¹ but abnormalities of gastric secretion have not been observed when groups of patients suspected of having food or other allergies have been studied.⁹²⁻⁹⁴

The presence of eosinophils in fecal mucus has been adduced as evidence favoring the allergic nature of certain diarrheal disorders,⁹⁵ particularly ulcerative colitis.⁶ Bockus,⁴³ on the other hand, writes, "cytologic examination of the stomach, bowel and rectal secretions has given little assistance in determining the etiologic basis of sus-

pected gastro-intestinal allergy." Before the significance of eosinophils in rectal discharges or mucus can be evaluated, further cytologic procedures, such as Bercovitz's⁹⁶ examination of rectal material in various intestinal disorders, appear necessary. Although eosinophilia is frequently associated with the body's reaction to foreign or altered protein, reactions of this type may be the result as well as the cause of a disease. Thus, a necrotic neoplasm may provoke eosinophilia,⁹⁷ and in a similar fashion, eosinophilia in a disease like ulcerative colitis may merely be the result of tissue destruction. If this is true, interpretation of eosinophils in rectal discharges is difficult.

SUMMARY

The experimental production in animals and man of reactions in the gastrointestinal tract due to contact of sensitized tissue with antigen (allergen) appears to be established. Evidence for the spontaneous occurrence of gastrointestinal allergy in man is good but not conclusive. The incidence of such reactions, assuming that they occur, cannot be determined at the present time for a number of reasons: the symptoms of so-called gastrointestinal allergy are common to many conditions and are prevalent in a considerable portion of the population; there are apparently no manifestations peculiar to gastrointestinal allergy alone, and the methods commonly used for diagnosis are not sufficiently accurate. The validity, in particular, of indirect tests, such as skin tests, changes in the number of blood cells or x-ray findings unaccompanied by symptoms cannot be assessed at present. These tests are reliable only to the extent that results can be correlated with proved gastrointestinal allergy, cases of which appear to be exceedingly rare.

Proof that a patient's gastrointestinal symptoms are on an allergic basis theoretically could be achieved if the following requirements were fulfilled: the symptoms should be caused by contact with a specific substance that is innocuous to the bulk of the population, an immune mechanism should be evident in their pathogenesis, and lesions or functional changes in the gut should be demonstrable. These requirements are difficult if not impossible to meet with present knowledge or techniques. However, it seems reasonable to make the diagnosis of gastrointestinal allergy if gastrointestinal symptoms invariably follow contact with a normally inactive substance, and if other causes such as psychic effects and mechanical irritation are excluded. Regarding foods, the following criteria are suggested: the food should be given in capsules by stomach tube or in such a manner that the patient is unaware of its nature, reproducible symptoms, signs or x-ray findings should consistently follow administration of the disguised food at a more or less constant interval possibly not to exceed a

few hours, other foods given to the patient in the same manner should not produce similar changes, and the suspected food given in the same manner to normal subjects should not cause the observed effects.

The fulfillment of these criteria for the diagnosis of gastrointestinal allergy would be a laborious procedure. If the diagnosis could be firmly established in a number of cases, a characteristic clinical pattern might become apparent and correlation with indirect tests might be possible.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 35351

PRESENTATION OF CASE

A thirteen-year-old boy was admitted to the hospital with the chief complaint of pain in the back and right leg.

Six months before admission the patient fell on the ice and struck his sacrum. For about a week he felt considerable pain, but then was asymptomatic for two months. Four months before entry he noted the sudden onset of a steady dull pain in his right groin associated with a temperature up to 102°F. He was admitted to a community hospital, where an appendectomy was performed. Apparently the appendix was normal. Almost immediately after discharge he complained of right lumbosacral backache, general malaise and nausea. The temperature rose to 102°F and he was readmitted to the hospital. The back pain radiated to the left, and he also complained of pain in and behind the right knee. Since then the pain had been more or less constant and was aggravated by movement and palpation. During this four-month period he noted weakness of the legs. He also had anorexia, weight loss, several episodes of epistaxes and easy bruising of the lips. He had recurrent fever with true chills, and frequent episodes of delirium. The past history was non-contributory.

Physical examination revealed a pale, emaciated boy complaining of pain in the right knee and back. There was no peripheral lymphadenopathy except for small shotty inguinal lymph nodes. The lungs were clear. There was a Grade II systolic murmur along the left sternal border. Examination of the abdomen disclosed tenderness in the left upper quadrant but no definite mass was felt. The liver edge was just palpable, and the spleen was not felt. A fleeting, spherical firm mass was palpable above the left inguinal ligament. Examination of the extremities revealed marked wasting of the legs and atrophy of both quadriceps.

There was tenderness along the sciatic nerve from the great sciatic notch to the calf, and to the right of the third and fourth lumbar vertebrae. The lumbar spine was fixed in slight flexion. The motion of the right hip was extremely painful. The patient walked with a slight limp on the right.

Neurologic examination revealed general weakness of the legs and arms and atrophy of both quadriceps. The deep reflexes were hypoactive. The plantar reflexes were down. Sensation was intact throughout. The eyes were normal except for slight blurring of the disks. There was no nystagmus — horizontal or vertical.

The blood pressure was 110 systolic, 80 diastolic. The temperature was 99°F, the pulse 100, and the respirations 22.

Urinalysis revealed no abnormality. The white-cell count ranged from 7700 to 4000, with a normal differential on admission changing to one in which 9 per cent of peculiar cells called "plasma cells" were found. The hemoglobin was 10.6 gm on admission. There was hypochromia, anisocytosis, poikilocytosis and polychromasia.

A bone-marrow aspiration of the first lumbar vertebra revealed on one of several stained specimens a sheet of abnormal cells that appeared to resemble plasma cells or malignant tumor cells.

The stools were guaiac negative. The total protein was 7.6 gm per 100 cc, with an albumin of 4.7 gm and a globulin of 2.8 gm. The nonprotein nitrogen was 24 mg, the calcium 10.1 mg, the phosphorus 4.9 mg, and the alkaline phosphatase 6.1 units per 100 cc.

The cerebrospinal fluid was normal. An electromyogram showed an abnormal record; there were spontaneous fasciculations in the muscles of the upper extremities.

X-ray examination of the chest and abdomen was negative. X-ray examination of the bones revealed diffuse granularity of all the bones of the lumbar spine and pelvis, suggesting demineralization. An area of destruction was disclosed in the body of the fifth lumbar vertebra and another in the left tenth rib in the axillary line.

The patient ran a low febrile course, with significant progressive weight loss and frequent episodes of lower lumbar pain extending down to the right leg. On several occasions he experienced severe crampy pain radiating from the thoracic spine. The pain was sufficiently severe to require the administration of morphine on several occasions.

On the twenty-fourth hospital day a segment of the tenth left rib was removed.

DIFFERENTIAL DIAGNOSIS

DR CHARLES S KUBIK. I think it should be stated that not only were the knee jerks weak but also there was a marked difference between the right and the left. The right was considerably weaker than the left.

few hours, other foods given to the patient in the same manner should not produce similar changes, and the suspected food given in the same manner to normal subjects should not cause the observed effects

The fulfillment of these criteria for the diagnosis of gastrointestinal allergy would be a laborious procedure. If the diagnosis could be firmly established in a number of cases, a characteristic clinical pattern might become apparent and correlation with indirect tests might be possible.

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DR KUBIK This clinical summary does not begin to indicate the difficulties encountered in making the diagnosis. There was a considerable difference of opinion among clinicians and radiologists regarding the significance of the x-ray findings, which now seem so clearly defined. The lesion in the rib was not discovered until after the patient had been in the hospital for some time. He looked very ill, he had lost weight, and nearly every movement resulted in pain, so that the question of generalized tumor involvement had to be most thoroughly investigated.

DR BAUER I wonder, since he had "plasma cells" in the smear, with similar cells having been found in the bone-marrow aspirations, why the surgeons chose to do a resection of the rib to be certain what they were dealing with. With that amount of evidence there must have been some question about the plasma cells, both in the smear and in the marrow.

DR FRANK B. NORBURY They were seen by several people, who were sure they were abnormal cells, and the term "plasma cell" was the most logical one for them. We thought that biopsy would give a more direct answer than aspiration alone.

DR L. S. P. DAVIDSON (Edinburgh) I think the cytology of these cells is important. The patient was suffering from some diffuse malignant process involving many bones. I do not believe the absence of Bence-Jones bodies or changes in the plasma protein rule out multiple myeloma. Fifty per cent of the cases at the time of diagnosis do not have these changes. On the other hand, the findings of anemia, weakness, pain and temperature are frequently noted. It seems to me that because of the malignant process in the bone marrow, the cytology becomes of great importance. I do not believe one should rule out multiple myeloma because certain features are not present. If we accept the finding of "plasma cells," one should consider it seriously. The plasma-cell increase in the peripheral blood — 9 per cent — is interesting, and I have only seen 1 case — that was my first case, twenty-five years ago — in which multiple myeloma was associated with plasma cells in the peripheral blood. We have diagnosed 40 or 50 cases by radiology followed by sternal puncture or, frequently, by sternal puncture alone. I think this patient may well have had multiple myeloma.

DR BENJAMIN CASTLEMAN Have you seen it in a patient this young?

DR DAVIDSON I only see patients from fourteen years of age up, so I would not be able to answer that.

CLINICAL DIAGNOSIS

Neuroblastoma?
Multiple myeloma?

DR. ROSS'S DIAGNOSIS

Neuroblastoma

ANATOMICAL DIAGNOSIS

Neuroblastoma metastatic, of rib

PATHOLOGICAL DISCUSSION

DR CASTLEMAN The rib biopsy demonstrated neuroblastoma — a classic one showing small cells with the characteristic grouping in so-called rosettes. It is interesting to recall that the neuroblastic origin of this tumor was first clearly proved in this building in 1910 by Dr. James Homer Wright,¹ then director of the laboratory, though the possibility of such an origin had been suggested by Marchand² as early as 1891. Until then they were called small-cell sarcoma or lymphoma, and it was Wright who described 5 cases and showed that the tumor cells produced nerve fibrils. Here are some of Dr. Wright's original lantern slides, showing the rosettes very clearly.

DR ROSS Would the finding in the bone marrow fit in with the picture one sees at autopsy?

DR CASTLEMAN I did not see the bone-marrow aspiration, but I think it is quite probable that neuroblasts may have been mistaken for plasma cells. Neuroblasts are pear-shaped cells and the nucleus is characteristically eccentric.

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CASE 35352

PRESENTATION OF CASE

A forty-five-year-old housewife entered the hospital complaining of pain in the right lower quadrant.

Six months prior to admission the patient noticed a mass in the lower abdomen, which grew steadily and rapidly until admission. During this period she had three attacks of pain in the right lower quadrant, the first two preceding her menstrual periods. The pain was sharp, moderately severe and nonradiating.

DR RALPH A ROSS In summary, we have a thirteen-year-old boy with an injury to the lower back, who was asymptomatic after a period of a week. Two months later, he had pain in the region of the injury, extending down the right leg, associated with recurrent fever, chills, delirium, anorexia, anemia and a hemorrhagic tendency, with evidence of neurologic difficulty as brought out by Dr Kubik.

Examination showed a basal systolic murmur in the heart, possibly due to the increasing anemia, and evidence of a lesion in the lower lumbar region, with probable involvement of the sciatic nerve on the right, a lesion in the left rib and a possibility of some intracranial or posterior orbital lesion to explain the blurring of the disks.

May we see the x-ray films?

DR STANLEY M WYMAN These films were taken on two different dates. In the first group the chest and heart appear within normal limits. There is definitely a destructive lesion in the left tenth rib as described in the protocol. It seems to be purely osteolytic, with no evidence of bone reaction. This particular film shows no evidence of expansion of the bone.

DR WALTER BAUER How about the ribs on the right?

DR WYMAN I think these are vascular markings that extend across the rib and create a pseudodefekt. I do not believe it is a true lesion in the rib. However, a diffuse granularity is seen throughout all the bones of the lumbar spine, pelvis and upper femur. In the films taken a month later the fifth lumbar vertebra shows a diffuse denseness throughout its entire body, with a suggestion of some irregular destruction of the anterior portion and possibly the lower posterior angle of the body.

DR ROSS Are there any films of the upper extremities?

DR WYMAN There are none available.

DR ROSS The patient had a traumatic injury six months before hospital admission apparently not related to his subsequent illness. However, one might consider that it had initiated the train of events that led to the symptoms bringing him to the hospital. I do not believe that injury would explain the picture we are dealing with.

Could infection have been the main factor in this picture? The systemic symptoms, the malaise and the fever certainly could all be explained on the basis of general infection. He had progressive

anemia. Could the bone lesions, the destructive lesions in the fifth lumbar vertebra and the tenth rib have been on the basis of localized infection? That does not, however, satisfy the description of the generalized granularity — the demineralization of the bones in the pelvis.

So far as neoplasms — localized neoplastic disease, such as Ewing's tumor or osteogenic sarcoma — are concerned, again, the fever, the systemic signs and the central-nervous-system signs would fit primary bone tumor with metastases. However, I think after a period of four months the x-ray diagnosis should have been more definite, and the normal serum phosphatase indicates a destructive lesion without new bone formation, which would be against the diagnosis of primary bone tumor. The widespread involvement of the bone marrow, as evidenced by the leukopenia, the progressive anemia and the hemorrhagic tendency, suggests a neoplasm, primarily involving the medullary tissue.

Hodgkin's disease comes up for consideration — a rare condition in the pediatric age group — in this case appearing largely in the medullary tissue. I do not believe it was Hodgkin's disease.

Multiple myeloma gives a picture of diffuse bone disease. A normal serum protein is against the diagnosis as is the fact that this is a very rare condition in childhood. Aleukemic leukemia would again explain the picture of the widespread medullary disease, the large lesions in the lumbar spine and rib. Vague masses in the abdomen could be explained on the basis of large areas of leukemic infiltration. The finding of "plasma cells" in the pleural fluid and the suggestion of similar cells seen in smears of bone-marrow aspiration make the possibility of a lymphatic leukemia of the plasma cell type a likely one. This disease, although it is rare, is sometimes seen in the pediatric age group as one of the chronic leukemias and may cause findings such as those described.

Another neoplastic disease that I should like to consider is neuroblastoma, the commonest of the bone diseases in children. It involves the retroperitoneal space, the orbits and the intracranial structures and is often evidenced mainly by involvement of the medullary tissue. Because of the statistical probability, I shall leave my diagnosis as neuroblastoma involving mainly the fifth lumbar vertebra and the tenth rib on the left side, with general spread to the medullary tissue.

blood might reach this size if it developed slowly. The elevated prothrombin time suggests that hemorrhage was possible, but such a condition is extremely unlikely. Pelvic inflammatory disease, with an abscess, could cause a tumor of this size, but this is also unlikely since if she had had pelvic inflammation for six months, she surely would have had other symptoms associated with this entity early in the illness. Something new or dramatic happened to this tumor just before this hospitalization, and tubal disease does not fit the picture.

Since we have eliminated the uterus and the tube, the tumor mass must have been in the ovary. When enlargements of the ovary are considered, endometriosis must be mentioned. This would have been an enormous endometrioma, but that is possible. Endometriosis, however, is unlikely in a para IV, since that disease—like fibroids—is usually seen in women who have two or less children. The mass could have been a dermoid cyst, pseudomucinous cyst, fibroma, ovarian cancer or any sort of ovarian tumor. Since we postulate that this mass was a tumor of the ovary, we now have to explain what happened to it to account for the symptoms that brought the patient to the hospital and made her so ill. There are three possible explanations: a twist of the cyst, with infarction, sepsis within a cyst, which occasionally occurs in the dermoid cyst, and hemorrhage into the cyst. The history does not state that the tumor increased markedly in size, but because of the elevated prothrombin time I think a sudden hemorrhage is the best explanation. I will narrow my diagnosis down to an ovarian tumor mass, possibly an endometrioma, with hemorrhage into it, to account for this clinical picture.

DR BENJAMIN CASTLEMAN: Dr Klemperer, would you like to comment?

DR FRIEDRICH W KLEMPERER: I cannot see any relation of the rheumatoid arthritis to the mass. I wonder what medication the patient had. It is

stated in the literature that salicylate medication, which patients with rheumatoid arthritis frequently receive, is sometimes associated with an elevated prothrombin time.

DR WILLIAM BECKMAN: Our problem with this patient was somewhat different from Dr Ingersoll's. She looked sick from the time of admission, and she did have severe chronic rheumatoid arthritis. While she was on the ward, she had a normal temperature for the first forty-eight hours and then began to develop this elevated temperature, which remained elevated. The problem, therefore, was to decide whether the fever was in any way related to the rheumatoid arthritis, which would have made surgery unwise. After a few days, having ruled out to the best of our knowledge any extra-abdominal cause for her fever, operation was performed. The preoperative diagnosis was infarction of a pedunculated fibroid.

CLINICAL DIAGNOSIS

Infarcted pedunculated fibroid

DR INGERSOLL'S DIAGNOSIS

Hemorrhage into ovarian tumor, endometrioma?

ANATOMICAL DIAGNOSIS

Torsion and infarction of ovarian fibroma

PATHOLOGICAL DISCUSSION

DR CASTLEMAN: This patient was operated upon by Dr Howard Ulfelder, who found a large right ovarian tumor that had twisted one and a half times on its pedicle. When received in the laboratory, the tumor measured 20 by 15 by 9 cm and was deep red. The surface was covered with recently thrombosed tortuous veins, and the pedicle, which was 3 cm in diameter, was also a collection of thrombosed vessels. On section the tumor was solid, soft and obviously infarcted. Microscopically it was a benign fibroma.

The third attack occurred on the morning of the day of admission and was similar to the others but considerably more severe. There were no other symptoms. The last menstrual period began eight days before admission and lasted six days, the duration and flow being considered normal. Menses occurred every twenty-eight days and were usually preceded by a slight mucoid discharge. There had been no weight loss, change of bowel habits, menorrhagia or urinary symptoms.

The patient had been married thirteen years and had four children ranging in age from twelve to four years. She had had fairly severe rheumatoid arthritis for the past ten years.

Physical examination revealed a moderately tender mass in the lower abdomen, extending to the level of the umbilicus. It was about the size of a five-months' pregnant uterus, and was only slightly movable. The abdomen was stretched over the mass, and spasm could not be accurately evaluated. Peristalsis was normal. On pelvic examination the cervix was normal. The uterus could not be defined, but the cervix was not fixed. The mass was easily palpable but too large to enter the true pelvis. The vaults contained no other tumors. There was a slight, white, stringy vaginal discharge. The chest and heart were normal.

The temperature was 98.6°F, the pulse 66, and the respirations 16. The blood pressure was 158 systolic, 84 diastolic.

The hemoglobin was 85 per cent, and the white-cell count 18,800. The urine was normal. A barium enema showed the terminal ileum displaced into the right upper quadrant by a mass in the lower abdomen. The colon was normal. An intravenous pyelogram was interpreted as being normal, except for some evidence of pressure on the lower ends of both ureters by a large irregularly outlined, homogeneous mass extending from the pelvis upward. No tumor cells were found by vaginal smear. A rabbit test for pregnancy was negative.

On the third hospital day the temperature rose to 101°F, and the pulse to 100. The prothrombin time was 29 seconds (normal, 19 seconds). The respirations remained normal. The abdominal mass became progressively more tender on each succeeding day. In a chest film taken on the fourth day there was a small linear area of increased density above the right leaf of the diaphragm laterally. The prothrombin time rose to 41 seconds, and the white-cell

count was 20,800. The temperature remained elevated between 100 and 103°F.

An operation was performed on the seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR FRANCIS M INGERSOLL. In the discussion of this case there are three outstanding things that have to be correlated. First we note that the patient had an obvious tumor mass in the lower abdomen of six months' duration. We do not know what this mass was but will try to make a diagnosis. The second important point is that some change occurred in the mass that caused pain and precipitated hospital admission. The third point is that her hospital course was characterized by fever, leukocytosis and prostration. An elevated prothrombin time was discovered, which may be significant and may help to explain what happened within the mass. The hospital course suggests sepsis, and the possibility of sepsis in the tube, ovary or appendix must be considered and will be discussed later.

I would like to see the x-ray films to discover if they will give any leads in this situation.

DR JAMES R LINGLEY. It is interesting to note that the appendix is well visualized, so that the possibility of acute appendicitis or abscess is well ruled out. The mass extends out of the pelvis up to the level of the second lumbar vertebra, with pressure on the ureters. The ureters are filled down to the level of the mass. On the barium-enema examination the terminal ileum is displaced upward, outlining the upper border of the mass. It states in the protocol that the mass was irregular, but I would say that throughout most of the examination it is fairly smooth and not lobulated.

DR INGERSOLL. The first problem is to try to decide what the mass was, or with which organ it was associated. The possibility that it was in the gastrointestinal tract is unlikely, the gynecologic system is much more probable. A tumor of the uterus of six months' duration would be either a sarcoma or a fibroid. Fibroids of this size rarely occur in women who have had four children, especially when the last pregnancy was only four years previous to the onset of symptoms, as it was in this particular case. The history of normal menses argues against a uterine tumor.

This tumor may have been a pathologic process associated with a fallopian tube. A tube filled with

blood might reach this size if it developed slowly. The elevated prothrombin time suggests that hemorrhage was possible, but such a condition is extremely unlikely. Pelvic inflammatory disease, with an abscess, could cause a tumor of this size, but this is also unlikely since if she had had pelvic inflammation for six months, she surely would have had other symptoms associated with this entity early in the illness. Something new or dramatic happened to this tumor just before this hospitalization, and tubal disease does not fit the picture.

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A LOGICAL PROPOSAL

THE Committee on Membership of the Massachusetts Medical Society has approved and will recommend to the Council a change in Chapter V, Section 2 (b) of the by-laws. As at present worded the section reads

(b) The secretary of a district society shall receive an application from a graduate of a discontinued medical school, a foreign medical school or any medical school not approved by the Council only when

The applicant has possessed a license to practice medicine in the United States or its territories for at least five years

The proposed change applies to the second paragraph, which would subsequently read

The applicant has possessed a license to practice medicine in the Commonwealth, and has conducted that practice in the district from which he makes application, for at least one year

The reasons for such a change are apparent and seem logical. There are now no unapproved schools in existence in the United States, the period of great influx of graduates of foreign schools is over and, in fact, the recent graduates of most foreign schools are not now permitted even to take the examination for registration in Massachusetts. This condition will probably prevail at least until the Council on Medical Education and Hospitals of the American Medical Association has had made the investigation that it is sponsoring of foreign schools and issued its report.

Observation of a physician by his local colleagues for a year is of much greater value as a criterion than any number of probationary years elsewhere.

A five-year probationary period entails an unusual hardship on a physician who, because of lack of society membership, is debarred from staff privileges in many hospitals. It defeats the purpose of the Gallupe Plan, under which graduates of foreign or unaccepted schools are accorded supervised staff privileges. It defeats, indeed, the very purpose of medical organization, which is to ensure the delivery of the best medical care available to the greatest number of persons possible.

A COMMON RADIATION HAZARD

IN THIS era of rapid scientific and technological advances and their practical applications to modern life, the physician has an added responsibility. More than ever he must be on his guard not only to diagnose the unforeseen pathologic patterns resulting from employment of new products and processes but also to protect the public if possible from their ill advised usage before untoward results occur.

The papers by Williams and Hempelmann published elsewhere in this issue of the *Journal* are examples of the type of diligence that must be observed in evaluating a newly commercialized device. From the careful data of Williams it is obvious that the use of such devices is not without danger. The variation of output and the protection provided among the apparatus tested varied widely. The amount of radiation received as direct

diation by the customer and as scattered radiation by the salesforce represents a real potential hazard. Certainly, no warning plate bearing the inscription demanded by the American Standards Association Code can assure any degree of safety. Attention is called to the fact that unattended machines have been observed in use by children and young adults to study not only the bones of the feet but also those of the hands.

For the average busy adult there is less danger than for a child. He requires fewer fittings and has less time to satisfy his curiosity. The growing child, with several changes in footwear a year, presents the problem, as pointed out by Hempelmann, for he is the one who will be exposed to unknown amounts of radiation throughout his life, particularly during the growing period, and the late changes to the skin and particularly to his epiphyseal development must be anticipated and prevented.

The average fitting for a pair of shoes will require a minimum of two exposures, one for the child to observe, and a second for the parent. A few of the latest machines have duplicate viewing facilities for child and adult. These exposures will increase directly with the number of pairs of shoes tried on, the number of relatives or friends present and the innate curiosity of the child. It will be the exceptional salesperson who will risk loss of a sale by strict observance of any so-called safety code. There is also nothing to prevent the customer from shopping around in other stores boasting these modern marvels of shoe fitting.

Supposing a child is exposed to an erythema dose — and Williams's data show that on several machines this is reached with a few exposures — the delay of a week or two before skin changes manifest themselves allows them to be unnoticed or at best to be attributed to irritating socks or hot feet. If this insult is repeated many times permanent skin damages not only result but also the danger of epiphyseal damage and resulting foot deformities is encountered.

Blood changes and damage to the sex glands are less likely to occur as a result of customer exposure, but they become a definite possibility among the salesforce of the store. Knowledge of the safe daily

amount of scattered radiation is far from complete. The maximum daily exposure thought to be safe has recently been scaled down from 0.1 r per day to 0.3 r per week as the result of studies made by the Advisory Committee on X-Rays and Radium.

The question raised by these papers is simply this: Are shoe-fitting fluoroscopes a necessity for the proper fitting of shoes or are they in effect sales promotional and of advertising value only — a form of window dressing? If the answer to the question is the latter they should be abandoned entirely. If the former answer is given, the strictest supervision is necessary, and unfortunately there is actually no safe method of making these restrictions work.

Fundamentally, the problem can be resolved only if machines, drugs and technics, particularly those giving off potentially dangerous radiation or having dangerous side reactions, are restricted in use to those whose training makes them competent to employ them.

THE CARE OF THE PATIENT

THE statement of the Committee on Diabetes of the Massachusetts Medical Society elsewhere in this issue of the *Journal* deserves careful attention, not only because it points out that valuable information concerning the discovery and treatment of diabetes will soon be available but also because it demonstrates an attitude that epitomizes the best in medical practice. Regardless of the present furore over the future status of medicine in the United States, the primary concern of the doctor is unchanged: the welfare of the patient comes first. The program outlined has no relation to propaganda for or against state medicine but the content of the message, which justifies the confidence of the patient in his physician, should be widely publicized.

In the midst of the present controversy, the proposed campaign is reassuring and edifying. The medical profession has not deviated from its ideal of service — the primary goal of ceaseless effort to find the best means of recognizing and curing disease. The tidings of what can be an immense forward step in the diagnosis and treatment of a

disease that is one of the major causes of death may well prove more effective than more emotional approaches to the public on the score of the future of medical practice organized medicine, not resting on its laurels or even emphasizing previous discoveries and achievements, is committed to progressive endeavor in all branches of the science of healing

Here, then, is information that may justifiably be incorporated in the educational program being conducted by the leaders of American medicine — to prove, to those who are ignorant of, or in doubt about, its aims, that to the medical profession the care of the patient comes first, if and how to regulate the service rendered are matters of secondary importance. The plan outlined, and others like it, may well affect the public's answer to the question of who is best fitted to control the practice of medicine

SEA-GOING ARMY

TO BE rocked in the cradle of the deep may yet become the pleasant experience suggested by the old song, according to the release earlier this year from the Department of the Army of the National Military Establishment. It may be that the sponsorship, by the Army Medical Department alone, of the now well known drug that acts as both a preventive and cure of seasickness implies a situation well in hand in the Navy, it may be that the boys in blue are simply willing to continue taking it on the chin and when the breezes blow to "generally go below."

Credit for the discovery of Dramamine, the salvation of those who go down to the sea in ships, belongs to Dr. Leslie N. Gay, of the Protein Clinic of Johns Hopkins University Hospital, and Dr. Paul Carlner, likewise a member of the Johns Hopkins staff. The United States Army Transport *Ballou*, loaded with more than 400 defenders of that which lies between the shining seas, provided the impressive clinical tests of the drug.

During an extremely rough passage in November, 1948, between New York and Bremerhaven, Germany, a total of 418 soldiers were treated with Dramamine. All were quartered in sub-level compartments. Complete relief from seasickness was obtained in 407 cases, with failure or only partial

relief in 11. No unpleasant symptoms resulted from the drug itself.

Various control tests were made. In the preventive study one group was given Dramamine, and another group sugar capsules on the same schedule. Of the men receiving Dramamine, none developed nausea, and only 2 of the 134 became dizzy. Of 127 men who received the sugar capsules, 35 became seasick within twelve hours. All were relieved when placed on the Dramamine.

Of those who had remained well on Dramamine, 41 developed seasickness after the drug was omitted, 40 of these recovered spectacularly when it was again administered. Other men on the ship became ill, 195 of them severely. Of this group 187 were completely relieved within an hour after taking the first dose of Dramamine.

It appears that this boon to humanity, a chemical cousin of Benadryl and Pyribenzamine, has robbed the ocean of at least one of its perils.

Perhaps it should have become a top military secret.

—Mrs. Elizabeth Dodd died at St. Stephens, New Brunswick, a few weeks since, at the age of 111 years. She was born on board a British ship of war in the Bay of Biscay — Ten days per annum is said to be the average sickness of human life.

Boston M. & S. J., August 29, 1849

MASSACHUSETTS MEDICAL SOCIETY



DIABETES DETECTION — A STATEMENT OF THE COMMITTEE ON DIABETES

THE existence of a large number of persons with diabetes undiagnosed and therefore untreated has been demonstrated by surveys not only in Massachusetts but elsewhere. There is need for the dissemination among physicians of information about the recent methods of treatment of diabetes by means of programs in district-society and hospital meetings. There is also a great opportunity and need to convey information to the public about the service the physician can give to patients with diabetes in all stages of the disease, but particularly

during the early stage. This affords an opportunity for carrying out the purpose of the National Education Campaign upon which the American Medical Association is now embarked. The purpose of this campaign is to demonstrate to the American people the services that physicians can render and are rendering to the American public in prevention of illness and the care of the sick.

The Committee on Diabetes of the Massachusetts Medical Society met in session on June 15, with representatives and presidents of fifteen of the district societies. They approved the program to be carried out in district societies aimed at disseminating information to the public by way of public meetings, the press and radio and at discovering patients with unrecognized diabetes so that they might come under medical treatment in doctors' offices and receive the benefits of modern treatment.

The Committee will have available an outlined plan for operation in any locality as well as printed material for distribution. A 16-mm, twenty-minute film in sound and color on diabetes for lay meetings has been prepared through the co-operation of the U. S. Public Health Service and the American Diabetes Association and will be available on loan through the office of the Massachusetts Department of Public Health. Strip films in color are also being prepared and will be available by loan to doctors for use in informing the public about diabetes and in treating patients.

New and simplified methods of self-testing, approved by the American Diabetes Association, will be available on sale at drug stores. These methods will make it possible for persons to make home tests of the urine following printed directions; these include advice to see the family physician for interpretation. Chemical materials for testing the urine will be provided by the manufacturers free of charge to any doctors' committee organized to carry out diabetes-detection programs, and approved by the district medical society, if application is made to the Massachusetts Committee on Diabetes, 8 The Fenway, Boston.

APPROVED BY VOTE

FRANK N. ALLAN
GEORGE BALLANTYNE
JOSEPH ROSENTHAL
JAMES TOWNSEND
PRISCILLA WHITE
HOWARD F. ROOT, *Chairman*

CORRESPONDENCE

FIRST PRINCIPLES

To the Editor: Dr. Alexander's article in the July 14 issue of the *Journal* certainly fills us all with horror. The editorial comment upon it is most appropriate. However, I wonder if we are sufficiently horrified. Do we not realize that the same ideology that Dr. Alexander describes has already been insidiously introduced to us and accepted by many of us?

Let us read again the article by Dean Sperry in the *Journal* of December 23, 1948, and the editorial pertaining to it. In that article euthanasia is discussed but not condemned. In fact, the woman who did away with her husband was considered fortunate because she suffered no remorse.

Let us get back to first principles. Most of us give lip service to God as the creator of life. Why then do we presume to usurp His authority over life, its beginning, its functions and its end? We seem to set ourselves up as gods to decide who should be born and when, who should be sterilized, who should have a lobotomy, who should be put out of his misery. If we believe in God, why not leave such things to Him?

We seem to have lost the idea that the children and the aged, the insane and feeble-minded, the sick and the weak offer us a means of working out our own eternal salvation. I am afraid that we look at them either as nuisances or as sources of revenue.

If a thing is good, why not call it by its true name? It is only when we want to make an evil thing seem good that we invent a euphemistic name for it. Therefore we have therapeutic sterilization, therapeutic abortion, planned parenthood and euthanasia.

If called by their true names — mutilation for the purpose of sterilization, murder of the unborn, prostitution of marriage and murder in the first degree — they would be instantly rejected as horrible. Are we so easily deceived by euphemistic terminology that we do not see that we are in danger of becoming fiends rather than physicians?

MARGARET C. McMANIS, M.D.

Orange, Massachusetts

STAIGE D. BLACKFORD

To the Editor: Dr. Staige Davis Blackford of Charlottesville, Virginia, professor of the practice of medicine at the University of Virginia Department of Medicine and chief of gastroenterology at the University Hospital died on July 17. He was well known in Boston and New England because of medical service at the Massachusetts General Hospital and because of his associations with many New England men during World War II as medical-service chief of the Eighth Evacuation Hospital in North Africa and Italy.

He came from an old and distinguished Virginia family of clergymen, physicians and educators. Among his forebears in the earliest history of the old Dominion were the thoughtful, liberal and moderate Southerners who opposed slavery in a practical way by freeing their Negroes and paving for their repatriation in Africa. When the Civil War arose, this liberal tradition did not prevent the family members then living from serving the Confederacy in many capacities.

Staige Blackford's life exemplified the family traditions of liberalism and of loyalty. His service to his country in both world wars to his university and to his profession was as unrenouncing as it was selfless. His modesty, his forthright honesty, his always good-humored facility in exposing cant and pomposity, his disregard of personal ends brought public and academic recognition — some of us think, too little and too late. This irked his students and friends but not himself. His genius was friendship and sociability. He encouraged many colleagues young and old in their training and careers in their research and in their medical writing. His intimates knew him best as a skillful but always amiable disputant and conversationalist who loved the night-long ceaseless argument. A host of friends and patients are witnesses that while he was among us he

— loved no darkness

Sophisticated no truth

Nursed no delusion

Allowed no fears"

ROBERT S. PALMER, M.D.

320 Dartmouth Street
Boston

BOOK REVIEWS

Index-Catalogue of the Library of the Surgeon General's Office United States Army (Army Medical Library) Authors and subjects Fourth series, Vol X, M-Mez 4°, cloth, 994 pp Washington United States Government Printing Office, 1948 \$4 25

The *Index Catalogue* was created by an Act of Congress in 1879 and began publication in 1880 and is now in the middle of the fourth series. The material in each series is arranged alphabetically by author and subject in one alphabet. The first series consisting of sixteen volumes, published from 1880 to 1895, was edited by Dr John Shaw Billings, who brought the library to life after the Civil War and started it on its great career. The succeeding editions have been edited by Robert Fletcher, Fielding H Garrison and Claudius F Mayer, the present editor. In the first series Dr Billings endeavored to present all the literature contained in the collections of the library, either in books and pamphlets or in periodicals and serials. The second series, of twenty-one volumes, covered the period 1896-1916, and the third series, of ten volumes, 1918 to 1932. The fourth series, now in process of publication, consisting of ten volumes, A-Mc, 1936-1948, lists 7214 authors of books and pamphlets and 68,766 subject entries of material contained in books, pamphlets and periodicals. The subjects and their subdivisions total 6943. The last volume contains a check list of abbreviated titles of current publications received and indexed since 1919. Beginning at least with the third series, the indexing and publication of items became selective and did not represent the total number of titles of articles contained in the Library. The total number of volumes published to date is 57, covering a period of sixty-nine years. The total number of printed entries comprise 3,357,755, and the manuscript and printed catalogs of the Library total nearly 5,000,000 entries. The Army Medical Library is probably the largest and greatest medical library in the world. Its *Index Catalogue* provides for the world the greatest medical bibliography of all time. The great catalogs of the British Museum and the Bibliothèque nationale in Paris are devoted to the listing of all the manuscripts, books and pamphlets contained in these libraries. They do not list periodical and serial articles. In 1879 Dr Billings began the publication of the *Index Medicus*, a current monthly periodical of medical literature. This continued through various trials and tribulations until 1927, when it consolidated with the rival list of the American Medical Association to form the present *Quarterly Cumulative Index Medicus*. At the present time the continuance of the catalog and the future of the *QCIM* are being considered by the top authorities in Washington and Chicago, and the fate of the catalog hangs in the balance. Much of the great reputation of the Army Medical Library is based on the *Index Catalogue*, and with its continuance or discontinuance this reputation will rise or fall as the case may be. Its discontinuance would constitute an overwhelming calamity, and the medical world would suffer a great loss. It is hoped that the decision will be favorable to its continuance.

On the Contributions of Hugh Owen Thomas of Liverpool, Sir Robert Jones of Liverpool and London, John Ridlon, M.D., of New York and Chicago to Modern Orthopedic Surgery By H Winnett Orr, M.D. With a supplement on *Ridlon and His Share in Moulding Orthopedic Surgery*, by Arthur Steindler 8°, cloth, 253 pp Springfield, Illinois Charles C Thomas, 1949, \$4 50

In this volume Dr Orr discusses the works and accomplishments of three great orthopedic surgeons, two British and one American. Preceding the text proper are biographies of Thomas, Jones and Ridlon. The text is divided into eight chapters including a review of past and present methods in surgical practice (a review of past and present methods of surgical treatment, preface to several of Thomas's more important books), rest as a fundamental factor in the relief of pain and the arrest and cure of inflammation (introducing the famous Thomas splint), methods of obtaining rest in fractures and in articular disease, diagnosis and treatment of hip disease, disease of the knee joint, foot and ankle, the prevention and cure of disability and deformity in fractures, comments upon methods still in use in orthopedic practice, from the writings of H O Thomas, Sir Robert Jones and Dr John Ridlon, and the influence of Hugh Owen Thomas, Dr John

Ridlon and Sir Robert Jones upon each other and upon orthopedic surgery. A supplement by Dr Arthur Steindler discusses Dr Ridlon and orthopedic surgery. An annotated bibliography concludes the text. The volume is well published, but the lack of an index and a table of contents detracts from its reference value. The book should be in all medical libraries and available to surgeons and orthopedists.

Fighting Spotted Fever in the Rockies By Esther G Price. 8°, cloth, 269 pp., with 165 illustrations and frontispiece Helena, Montana Naegle Printing Company, 1948 \$4 00

In this popular book the author relates the story of the struggle to control and prevent Rocky Mountain spotted fever in Montana. The campaign began in 1901, and was continuously hampered by professional jealousy, hostility by large real-estate interests, politics and nonco-operation of the population. In 1913 the State passed an act establishing a board of entomology that eventually obtained the co-operation of the federal authorities, leading to concentrated research and the identification of the virus of the disease and the discovery of the Spencer-Parker preventive vaccine. From the first makeshift woodshed laboratory to the modern Rocky Mountain Laboratory at Hamilton, Montana, has been a long and dangerous journey, a number of the staff succumbing to the disease. The laboratory today produces annually vaccine enough for 140,000 persons in the United States, Canada and Brazil.

The disease was originally found in the western states from the Canadian border to Nebraska and extending to the eastern portions of the Pacific Coast states. It has now spread to the Middle Atlantic states. Today, there are only six states in which the disease has not been reported: Maine, Vermont, Rhode Island, Connecticut, Michigan and Kansas. Three ticks have been proved transmitting agents of the virus of the disease: the Rocky Mountain wood tick, the American dog tick, and the rabbit tick, the three together having a wide distribution throughout the United States, Canada and Alaska. Because of existing conditions, it will not be possible to eradicate the ticks completely, but the vaccine provides effective protection for exposed persons.

An appendix gives the state laws of Montana of 1913 and 1919 affecting tick-control work in the Bitter Root Valley. The text concludes with a bibliography, and there are indexes of names and subjects. The story of this dramatic campaign is told in an interesting narrative style. The book should be in all medical libraries and in all medical-history collections.

NOTICES

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held in the classroom of the Nurses' Residence on Thursday, September 8 at 7 15 p m. Cases will be presented and discussed by Drs R Adelaide Draper, Constance Curtiss and Clara Waldinger. Dr Eliza A Melkon will be chairman.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A regular meeting of The New England Society of Anesthesiologists will be held in the auditorium of Building A Boston University School of Medicine, Boston, on Tuesday, September 13, at 8:00 p m.

A round-table discussion entitled "Respiratory Problems in Acute Poliomyelitis" will be conducted by Drs William Berenberg, Carl G Flake, David Grice and Stanley Sarnoff. Dr Robert M Smith will be moderator.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

Four sessions on research in medicine will be held in the Statler Hotel, New York, on December 28 and 29 as part of the 116th meeting of the American Association for the Advancement of Science.

These sessions are under the sponsorship of AAAS Section N, of which Dr Gordon K Moe, University of Michigan, is secretary.

(Notices concluded on page xviii)

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THE PROFESSIONS IN THE SOCIETY OF TODAY*

ROSCOE POUND, LL D †

IN THE good old pioneer days in one of the younger western commonwealths a man conceived the idea that by putting a magnet in a box of ointment and leaving it there overnight he could produce a "magnetic ointment" with marvelous powers. He impressed a community with the value of his magnetic ointment and soon did a considerable business in making and selling it. On this he built up an extensive practice in the way of consultations with the ailing and prescribing different methods of using and applying the ointment according to the nature of the difficulty. Then came a statute requiring those who practiced medicine to take an examination and procure a license, and the old man, having neglected these formalities, was prosecuted and convicted of practicing medicine without a license. In passing sentence the trial judge spoke severely about amateur prescribing of quack remedies as a menace to the general health. At this the old man broke in protestingly. He said "Your Honor is calling me an amateur? Why, I have made more money in my business each of the last five years than all of any three licensed doctors in the county put together."

Undoubtedly the professional athlete, whose type is perhaps the professional baseball player, has confused popular ideas in this connection. The distinction between the professional and the amateur, of which we hear so much in the absorbing interest of sport, has done much to make a profession denote a money-making activity. In fifty years of teaching of law to students in the face of modes of thought engendered by sport, I have not found it easy to impart the conception of a group of men pursuing a common calling as a learned art and as a public service — nonetheless a public service because it may incidentally be a means of livelihood. From the Middle Ages the formative era of our social institutions, we had received this idea of a profession and medicine, the law, the ministry and teaching had grown up to its pattern. The conservatism of the universities and of professional schools on their model, and the inherited spirit of the apprentice training, which for a time succeeded

academic teaching of medicine and law in England and America, transmitted this idea to our time, and our books are full of it. But the idea was sorely tried under the reign of pioneer modes of thinking in nineteenth-century America. Moreover, many important callings have been claiming to rank with the older recognized professions as learned arts, taught in universities and pursued in a tradition of learning. Such are at least journalism, engineering, business administration, social work and public administration. In addition, almost all callings and activities have become organized and are pushing for every kind of recognition. Thus, we must inquire how far our older idea of a profession may be stretched to include socially or economically important callings of today and how that idea, stretched or not, is affected by the rise of the service state and its consequences in the society of the time.

Let me repeat what we mean by the term profession when we speak of the old recognized professions. We mean an organized calling in which men pursue a learned art and are united in the pursuit of it as a public service — as I have said, no less a public service because they may make a livelihood thereby. Here, from the professional standpoint there are three essential ideas — organization, learning and a spirit of public service. The gaining of a livelihood is not a professional consideration. Indeed, the professional spirit, the spirit of a public service, constantly curbs the urge of that instinct.

It is no disparagement of honorable trades and callings, which when properly carried on render real public service, to insist that an organized profession of physicians or of lawyers is not primarily analogous to a retail grocers' association and that there is a generic distinction between a medical society or an organized bar and a plumbers' or lumber dealers' association. It is unhappily true that there was in the last century in America a tendency to deprofessionalize the old professions, to reduce all callings to the level of individual business enterprise, and to think of medical societies or bar associations as like trade organizations. But the root purpose is different. The trade association exists for the purposes of the trade as a money-making

*Presented at the annual meeting of the Massachusetts Medical Society, Boston.

†University Professor Emeritus Harvard University formerly dean Harvard Law School.

activity The medical society exists primarily for the purposes of medicine, not of the doctor of medicine, and for the advancement of the healing art. The bar association exists primarily for the purposes of the law rather than of the lawyer and for advancement of the administration of justice according to law. Lord Darling spoke of certain legislation enacted at the instance of trade organizations as intended to relieve the members of those organizations from the humiliating position of being on an equality with the rest of the King's subjects. An organized profession, on the other hand, seeks no such legislation relieving it of duties incumbent upon it. It does not seek to advance the money-making feature of professional activity but seeks rather to make as effective as possible its primary character of a public service. What medical associations have done for advancement of medicine I need not recount to you. But I may remind you that bar associations have in the present generation lifted the standard of professional education, codified professional ethics, promoted uniformity of commercial law, and brought about simplification of legal procedure and removal of archaic technicalities. An engineer may patent his invention. A manufacturer may protect his trade secret or patent his discovered process. What a member of a profession invents or discovers is not his property. It is at the service of the public.

A tradition of duty of the physician to the patient, to the medical profession, and to the public, a tradition of the duty of the lawyer to the client, to the profession, to the court, and to the public, authoritatively declared in codes of professional ethics, taught by precept and example and made effective by the discipline of an organized profession, makes for effective service to the public such as could not be had from individual practitioners not bred to the tradition and motivated, as in a trade, primarily, if not solely, by quest of pecuniary gain. Nor can this professional tradition be replaced with benefit to the public by a political tradition of officeholders owing primary allegiance to political parties and depending for advancement on the favor of political leaders. Moreover, the professional organization and tradition are even more to the public interest in their effect on the learned arts than the professions follow as callings.

All advance in science, in arts, in learning, in short, all progress in civilization—in the raising of human powers to their highest possibilities—is the result of trial and error, that is, of experimentation. Every physician, every hospital, every lawyer, every law school, every teacher can and is impelled to experiment and invent, and as the professional spirit of public service leads to promulgation of the results of experiment and invention and putting the results freely at the service of others, they are not individual trade secrets and are not patented, they do not need to be argued to bureaus,

nor do those who would use them have to await official adoption of them. They are open to free use and make their way on their intrinsic merit.

Huge bureaus of graduates of medical schools and of law schools, brought up to seek public office and organized in the civil service as public employees, can be no effective substitute for the professions.

Unhappily, the public interest in having a body of practitioners of medicine and of law imbued with the spirit of a profession and by training and organization and discipline held to high standards of professional conduct was not so clear in pioneer America as it is today. The idea of a profession seemed repugnant to rising American democracy. The feeling was strong that all callings should be on the same footing, namely, the footing of a business—of a money-making calling. To dignify any calling by holding it a profession, and to prescribe high qualifications for and limit access to it, seemed undemocratic and un-American. Moreover, pioneer America distrusted specialists. Faith in versatility was pre-eminently an article in the pioneer's creed. In consequence, there was a general rejection of the idea of a learned, responsible, self-governing profession. You know what the situation was in medicine when in 1910 the American Medical Association with the help of the Carnegie Foundation took medical education in hand. Let me tell the story of the law to make the point further. Some states threw the practice of law open to nonlawyers, with bad effects on legal procedure some of which are still manifest, and, indeed the legal osteopath and legal chiropractor and legal faith healer have been as favored by American legislators as have their medical counterparts. Some states that retained a requirement of admission to the bar provided that anyone was to be admitted with no other qualification than lack of a conspicuously bad character. All the states, by legislation or by increasingly lax administration of their requirements and lack of public or professional interest in the matter, made entrance upon practice easy with a minimum of qualification. As population increased, and large numbers of lawyers were admitted in great urban centers, discipline became lax, and many forensic abuses, such as offensive conduct toward witnesses and abuses in the fomenting of litigation, grew up. As the practice of law was regarded as only a business, organizations grew up in large cities in which lawyers, physicians, runners and even professional witnesses came to be engaged in preying alike upon the victims of accidents and those responsible for accidents. Experience taught us the value of the professional tradition and of the distinction between a profession and a trade. Reprofessionalization has gone forward steadily for two generations.

But reprofessionalization had hardly been achieved when the idea of a profession began to be subjected to new pressure.

From the beginning, American political thought had been dominated by fear of governmental oppression of the individual. Those who colonized America had been brought up in an atmosphere of resistance to the centralized personal government of the Tudors and Stuarts, and experience of arbitrary government of the colonies from Westminster had strengthened their feeling. Coincident with the movement for reprofessionalizing the old professional callings, however, there has been a change in the American attitude toward government. In a recent book Professor Corwin has written of the decadence of the fear of governmental oppression. Throughout the world the present century has seen a steady rise of the idea of the service state — the state that performs all manner of services for the people instead of leaving them as free as possible to serve themselves or to procure services for themselves according to their individual ideas of what they need or what they wish. I am not here to speak against the service state. In an age of big-ness other interests than the social interest in the general security press for recognition, and the state that merely keeps the peace and maintains order does not satisfy. But with the multiplication of services rendered by the state comes a multiplication of officials, and ideas of official omniscience and majority infallibility come also. When every form of public service becomes at least potentially a state function, the difference between a public service performed by a profession and a public function performed by a bureau becomes crucial. The one becomes a matter of free enterprise, and the other one of politically regimented activity.

Accordingly, I seem to see four sources of menace to the professional ideal in the society of today. One, the exigencies of the individual economic existence, has always been with us. It is simply magnified in the crowded world of the time. A second is the multiplication of detail in every branch of learning, and notably in the learned arts pursued by the members of a profession. Nowadays these details are multiplied beyond what the individual practitioner can hope to master completely. There is consequent need of co-operation of practitioners leading to partnerships of increasing size and conceivably even to corporations in which individual responsibility may become merged. Thirdly, when this stage has been reached it is difficult to resist the pressure of business methods, which easily become the methods of competitive acquisitive activity. Fourthly, all this goes along with and is given impetus by the advent of the service state and consequent growing tendency to rely on official rather than on individual private initiative and to commit all things to bureaus of politically organized society.

Let me illustrate from the legal profession what you can no doubt duplicate from your profession,

the difference between the last century and the present.

In November, 1890, two farmers in the county where I had been admitted to the bar, being advised each by his lawyer that a doubtful point of law was decisive of their dispute and that if litigated it would have to be taken to the Supreme Court for final determination, agreed to submit the question of law to the opinion of a well known lawyer in the capital of the state from which they both had come. Accordingly an agreed statement of the facts, which were not controverted, was drawn up, and I was sent with it by agreement of the parties to obtain the desired opinion. The lawyer whose opinion I was to get was one of the leaders of the bar in not the least of the states of the Middle West. His office around the corner from a main street of the capital city, was a one-story brick building from which there hung over the sidewalk a small, weather beaten sign, "Notary Public." Going in at the front door I found a room furnished with the wooden cuspidors of the period and old-fashioned chairs such as we used to see on the sidewalks in front of country hotels, and with the walls lined with bookcases extending to the ceiling and full of books. There was a long table in the middle of the room with law books and a Webster's Dictionary on it. In one corner there was a combination desk and bookcase at which sat one whom I took to be a clerk. In another corner one whom I took to be a student "reading law," as the phrase then was, had a book open before him. Having stated my business to the clerk, I was soon admitted to the inner office, which was furnished much as the outer room. The lawyer presently looked up from some papers he was reading and said he was at my service. I handed him the agreed statement of facts and explained that his written opinion on their legal effect was desired. He asked if there was any statute on the subject in the state from which I had come to him. I told him there was not, nor had the question of law been passed on by the Supreme Court of that state. It was a question of common law, and hence his written opinion was desired. He looked over the statement of facts once more, tapped the table with his fist a few times, pulled a few sheets of legal cap paper out of a drawer and then and there wrote out by hand a three-page opinion in ink, which he handed me. I had come prepared to pay a fairly large fee, but he had endorsed a relatively small one on the opinion and when I paid it he receipted it in the same place. Such was the office of a leader of the bar in the consulship of Plancus.

A few years ago a lawyer from a rural county-seat in Maine had occasion to call upon one of the leaders of the bar in Boston. Going up in the elevator in a large office building he found the leader's firm occupying two floors. There was a great room like a court, where he went in. Around it were

office rooms on all sides and above were more rooms all around on a balcony. In the middle of the court-like space was a desk in charge of a "receptionist." Typewriters were clicking all about, many people were seated about the room, and many were hurrying in and out of the office rooms. The astonished country lawyer went up to the receptionist and said "I want a room with bath."

It is not easy to maintain the professional ideal in such an atmosphere of a great law factory. What keeps it alive is the professional tradition. But one may question whether it could be kept alive if for the metropolitan law office we were to substitute a huge government bureau. Certainly the ideal is strained in the legal departments of some great public utilities with their staffs of lawyers, law clerks, investigators and experts. Some great industrial enterprises have such legal departments also. Whether medical departments approaching this have been growing up I do not know. At any rate, the tendency of our economic development, as it affects the legal profession, is to bring about something very like a class of employees of corporations called law clerks who may yet be seen forming a law clerk's union affiliated with the CIO, and exerting themselves not to advance the administration of justice but to advance the compensation of law clerks. An incidental bad effect of this course of development of the metropolitan lawyer is that the bar often comes to be divided into two classes, habitual plaintiff's lawyers and habitual defendant's lawyers, each with its staff of lawyers, law clerks, experts and, one suspects, witnesses. Already we have great administrative bureaus of the national government and of state governments, each often with its legal and medical and technical staff.

Economic expansion, the growth of industry, the multiplying of metropolitan cities and the new relations calling for adjustment and new problems of ordering the conduct of enterprises and the relations involved in them have called for the type of office I have described. It is a natural and inevitable response to them. But even more the professional ideal is menaced by the development of great government bureaus and a movement to take over the arts practiced by the professions and make of them functions of the government to be exercised by its bureaus in a superservice state that may become a service super-state. For the idea of a profession is incompatible with performance of its functions or the exercise of its art, by or under the immediate supervision of a government bureau. A profession postulates individuals free to pursue a learned art so as to make for the highest development of human powers. The individual servant of a government exercising under its supervision a calling managed by a government bureau can be no substitute for the scientist, the philosopher, the teacher, each freely exploring his chosen field

of learning and exercising his inventive faculties and trained imagination in his own way, not as a subordinate in a bureaucratic hierarchy, not as a hired seeker for what he is told to find by his superiors, but as a free seeker for the truth for its own sake, impelled by the spirit of public service inculcated in his profession.

If all callings are but money-making activities and making of a livelihood is their primary concern, it follows, in an economic order in which the great majority of the community are on the payroll either of the government or of some corporation, public, public service, charitable, or private, that most of us are in a sense employees and so liable to be caught up in a regime of employees' organizations, collective bargaining over wages and strikes. Organization of physicians for advancement of medicine, organization of lawyers for advancement of the administration of justice and organization of teachers for the advancement of teaching must give way to organization of employees of every grade and kind of employer for the advancement of wages and dictation of the conditions of employment. Already the two major labor organizations are carrying on a campaign to unionize the "white-collar workers" in industry and business. This may well presently take in the younger members of the bar in the legal departments of large companies. Already the American Federation of Labor has organized municipal employees, and in Los Angeles the probation officers, whom we had been thinking of as members of a rising profession of social workers, are members of the Probation Officers' Union, a branch of the Municipal Employees' Union, affiliated with the national organization. The National Labor Relations Board held and was upheld by the Supreme Court of the United States in holding that plant guards during the war, enlisted at first as soldiers and later made part of city police forces, could be organized in unions by the Congress of Industrial Organizations. Are the young lawyers in the office of a city attorney, along with the clerks and stenographers, the municipal probation officers, the clerks, secretaries and typists in the various city departments, the firemen and the policemen, to be in a union of municipal employees and from time to time to strike for increased pay as collective bargain contracts expire or when one of their number is removed or discharged? Next, county employees may be organized as such so that the clerical force in the courthouse may go on a strike and tie up the administration of justice. Are the assistant district attorneys to be unionized also? May we not see unions of state employees and find the secretaries of the judges of the Supreme Court striking? Already there are unions of federal employees, and these may come to include the young men, members of the bar, who are secretaries to the justices of the highest court in the land. Every department and major ad-

ministrative agency of the federal Government has many lawyers on its roster. Unions of federal employees will seek to include them. Moreover, the law reports show that the courts have come to be much troubled to determine whether and when physicians in a hospital are independent contractors and when they are employees of a charitable corporation.

Teachers in the public schools have been unionized in more places than one, and members of university faculties are now active in a teachers' union in some of our old historic institutions. Are we to see closed shops of higher learning with union faculties collectively bargained with, check off for union dues and all the concomitants of organized pursuit of higher wages in what had been thought a learned profession?

Thus as things are coming to be in an era of bigness, large-scale organization of all activities and strenuous acquisitive competitive self assertion the professional idea must contend with the rise to power of organizers of an expanding class of employees. Thus more and more as things are, as individuals in the professions have come to be regularly retained or nowadays regularly employed by great corporations or appointed to substantially permanent positions under the federal Government or state and municipal governments and administrative agencies a constantly larger number of practitioners in their capacity of employees are enlisted in organizations with the trade spirit of emphasis on wages rather than the professional idea of pursuit of a calling in the spirit of public service. Unless we are vigilant it may well be that this prevailing of the trade idea will make straight the path toward absorption of the professions in the service state. The course of that path is not hard to plot. We can see three possible stages: unionizing of all callings that may be taken to involve employment, at least so far as some in the calling are not capable of classification as employers, assumption of control of professional education by government subsidies and thus subordination of the professions to bureaucratic management, attempts to bring cheap and equal professional assistance to everyone's back door by government taking over of the callings pursuing learned arts. Such a consummation may be pictured as a carrying of the idea of the service state to its furthest logical development. The service state began by performing a few major services. In time it has undertaken more and more. Now it seems jealous of public service performed by anyone else. The advocates of the omniscient state will say that in primitive or pioneer societies certain public services are rendered by anyone who seeks to try his hand on the basis of such qualifications as he deems sufficient. Later as society advances such services are rendered by well qualified practitioners organized in professions,

the qualifications, as these professions develop, being prescribed and ascertained by governmental authority. Ultimately, it will be said, as political organization of society reaches maturity, all public services of every sort are to be exclusive governmental functions to be exercised by government bureaus.

Very likely, not all those who are teaching or preaching the doctrine of the super-service state will at the moment admit this conclusion. But I submit that before we go far with them on the path in which they are marching we should pause to see whither it leads. It should be remembered that the rise of the totalitarian state was coincident with the general reception of the idea of the service state and that both have Marxian socialism in their pedigree. Each in its way postulates an omniscient administration by supermen. If experience may be vouched that means in the end supermen under the direction of an *ex-officio* superman.

But leaving aside the question of the effect upon our American constitutional democratic polity of carrying the idea of the service state to its furthest development, let us look more in detail at the effect of that idea, as it is being urged, upon the professions.

Practice of medicine and practice of law the ministry and teaching are each of them essentially an individual learned art. Each is an art in which the individual approach of a skilled practitioner to the task immediately in hand is of first importance. He can not be made to a model so that every one can have the benefit of a professional man exactly as good for every purpose as everyone else has. The required combination of training, native skill and experience makes each practitioner in some measure and in varying degrees unique. No bureau and no super-administrator at a center of government, especially in a country of continental extent like our own, can co-ordinate all medical treatment, all medical research, all advocacy, all juristic inventiveness, all spiritual help or preaching, or all teaching, so that every locality and every citizen shall have the same advantages as every other. The professional ideal however, promotes effective individual treatment, individual counsel and forensic exertion, individual ministry and individual teaching, to the best of the powers of the individual practitioner, minister or teacher. Such things do not lend themselves to paper reports and mechanically produced uniformity and equality. The attempt to produce them may reduce the performance of the highest skills to a lower level of performance without raising the quality of lower skills or lesser experience. Uniform governmental management would sacrifice the reality of the public service sought to the exigencies of statistical and bureau-chart methods.

Government-managed religion was given up centuries ago. But centralized government manage-

office rooms on all sides and above were more rooms all around on a balcony. In the middle of the court-like space was a desk in charge of a "receptionist." Typewriters were clicking all about, many people were seated about the room, and many were hurrying in and out of the office rooms. The astonished country lawyer went up to the receptionist and said "I want a room with bath."

It is not easy to maintain the professional ideal in such an atmosphere of a great law factory. What keeps it alive is the professional tradition. But one may question whether it could be kept alive if for the metropolitan law office we were to substitute a huge government bureau. Certainly the ideal is strained in the legal departments of some great public utilities with their staffs of lawyers, law clerks, investigators and experts. Some great industrial enterprises have such legal departments also. Whether medical departments approaching this have been growing up I do not know. At any rate, the tendency of our economic development, as it affects the legal profession, is to bring about something very like a class of employees of corporations called law clerks who may yet be seen forming a law clerk's union affiliated with the CIO, and exerting themselves not to advance the administration of justice but to advance the compensation of law clerks. An incidental bad effect of this course of development of the metropolitan lawyer is that the bar often comes to be divided into two classes, habitual plaintiff's lawyers and habitual defendant's lawyers, each with its staff of lawyers, law clerks, experts and, one suspects, witnesses. Already we have great administrative bureaus of the national government and of state governments, each often with its legal and medical and technical staff.

Economic expansion, the growth of industry, the multiplying of metropolitan cities and the new relations calling for adjustment and new problems of ordering the conduct of enterprises and the relations involved in them have called for the type of office I have described. It is a natural and inevitable response to them. But even more the professional ideal is menaced by the development of great government bureaus and a movement to take over the arts practiced by the professions and make of them functions of the government to be exercised by its bureaus in a superservice state that may become a service super-state. For the idea of a profession is incompatible with performance of its functions or the exercise of its art, by or under the immediate supervision of a government bureau. A profession postulates individuals free to pursue a learned art so as to make for the highest development of human powers. The individual servant of a government exercising under its supervision a calling managed by a government bureau can be no substitute for the scientist, the philosopher, the teacher, each freely exploring his chosen field

of learning and exercising his inventive faculties and trained imagination in his own way, not as a subordinate in a bureaucratic hierarchy, not as a hired seeker for what he is told to find by his superiors, but as a free seeker for the truth for its own sake, impelled by the spirit of public service inculcated in his profession.

If all callings are but money-making activities and making of a livelihood is their primary concern, it follows, in an economic order in which the great majority of the community are on the payroll either of the government or of some corporation, public, public service, charitable, or private, that most of us are in a sense employees and so liable to be caught up in a regime of employees' organizations, collective bargaining over wages and strikes. Organization of physicians for advancement of medicine, organization of lawyers for advancement of the administration of justice and organization of teachers for the advancement of teaching must give way to organization of employees of every grade and kind of employer for the advancement of wages and dictation of the conditions of employment. Already the two major labor organizations are carrying on a campaign to unionize the "white-collar workers" in industry and business. This may well presently take in the younger members of the bar in the legal departments of large companies. Already the American Federation of Labor has organized municipal employees, and in Los Angeles the probation officers, whom we had been thinking of as members of a rising profession of social workers, are members of the Probation Officers' Union, a branch of the Municipal Employees' Union, affiliated with the national organization. The National Labor Relations Board held and was upheld by the Supreme Court of the United States in holding that plant guards during the war, enlisted at first as soldiers and later made part of city police forces, could be organized in unions by the Congress of Industrial Organizations. Are the young lawyers in the office of a city attorney, along with the clerks and stenographers, the municipal probation officers, the clerks, secretaries and typists in the various city departments, the firemen and the policemen, to be in a union of municipal employees and from time to time to strike for increased pay as collective bargain contracts expire or when one of their number is removed or discharged? Next, county employees may be organized as such so that the clerical force in the courthouse may go on a strike and tie up the administration of justice. Are the assistant district attorneys to be unionized also? May we not see unions of state employees and find the secretaries of the judges of the Supreme Court striking? Already there are unions of federal employees, and these may come to include the young men, members of the bar, who are secretaries to the justices of the highest court in the land. Every department and major ad-

surgeons' strikes, or lawyers' strikes, or ministers' strikes, which are foreshadowed by the impairment of the professional idea and the dominance of the idea of all callings as mere means of gaining a livelihood. Even less does the rise of the service state require to lead to setting up of the totalitarian state. Here, too, a balance is required, however easy it may be to go, as man is so likely to go, from one extreme to the other and then back again.

After all the individual man is the moral, social and legal unit. Certain of his activities may be organized in groups and associations and political societies. But his personality is not merged in any of them. Recognition of the moral worth of the individual human being is the great achievement of the political and juristic philosophy of the eighteenth and nineteenth centuries. Appreciation of the social interest in the individual life is the significant achievement of the social philosophy of the present generation. It is not likely that any

political or economic order that may supervene in such time as we can foresee will succeed in putting down the individual self-assertion that has been a motive force of progress. But the attempt to put it down with a sole eye to regimented co-operation may do a great deal of harm.

There has always been a human tendency to worship rulers. Today, majority dictation is often revered as the monarch's arbitrary dictation was in the seventeenth century. Lord Acton tells us that all power corrupts, absolute power corrupts absolutely. Majority-dictated science, majority-dictated philosophy and majority-dictated teaching take us back to the absolute rulers whom we set up majority rule to overthrow. The service state is a political step forward. But we must not let it turn back upon itself and lead us to absolutism. There is no surer route to absolutism than an unchecked omniscient bureaucracy.

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Since then quite an extensive literature has accumulated concerning this comparatively infrequent process. It is now well established that "pseudomyxoma peritonei" is not a disease in itself but an unpredictable complication occurring in the course of a variety of intra-abdominal conditions, including ovarian cyst-adenoma, mucocele of the appendix, omphalomesenteric cyst, intestinal diverticulum and retroperitoneal cystadenoma. Most unusual in this respect is the case described by McCrac and Coplin,³ in which the condition developed as a sequel to a gall-bladder carcinoma.

For a clear understanding of the process two main problems must be considered:

The first concerns the retention of the mucinoid material in the secreting viscus.

Obstruction of the appendiceal lumen and inability of the appendix to empty itself have been considered responsible for the mucocele of the appendix.² As the glands in the appendix continue to secrete, the organ gradually becomes distended with mucus. The resulting increase in internal pressure leads to thinning and eventually to rupture of the walls of the appendix, with resulting extrusion of the mucous content into the peritoneal cavity. The experimental work of Grodinsky and Rubnitz⁴ and of Rubnitz and Hermann⁵ has contributed considerable information explaining this sequence of events. This applies also to the "pseudomyxoma peritonei" resulting from the obstruction and rupture of an intestinal diverticulum.⁶

As for the "pseudomyxoma peritonei" of neoplastic origin the accumulation of secretion within the tumor mass is self-explained by the intrinsic nature of the process.

More difficult to understand is the second problem, the one concerning the continuation of secretion of the matter, whatsoever its source, escaped within the abdominal cavity. Many theories have been advanced to explain this point, but the one still most favorably accepted is Fraenkel's² original view of a seeding of the peritoneal membranes with secreting cells, subsequent cellular proliferation and mucous secretion.

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Under a system by which local funds for research or for teaching are derived from the national capital even the small part allocated to a locality imposes a kind of censorship on the local authorities. In their eagerness to share in the governmental distribution local officials are loth to make statements or espouse ideas out of conformity with the political or economic doctrines or aims of the central administration or in conflict with the scientific doctrines that its bureaus advocate. Government propaganda goes on upon a large and increasing scale, and dissent is silenced. The effect of this upon a learned art pursued in the spirit of a public service cannot fail to be destructive. How can scientists disagree with the government-promoted doctrines, how can advocates stand up against arbitrary bureaucratic administrative action, how can teachers teach the truth against officially approved doctrines when disagreement means failure to get government grants for research or government subsidies for the institution in which one is employed, or government appointments or assignments to salaried positions?

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Understand me. I am not preaching against the service state in itself. The society of today demands services beyond those which the state that only maintained order and repaired injuries could perform. Administrative agencies of promoting the general welfare have become a necessity and are with us to stay. It would be futile to quarrel with the idea of a service state kept in balance with the idea of individual spontaneous initiative characteristic of the American. What one must resist is

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I have often compared this problem of politics and law to the task of the juggler in the circus who keeps a succession of glass balls in the air at once, back and forth from his hand, never losing sight of any nor giving any one too exclusive attention. We have such a problem in the rise of the service state. Its requirements and its logical limits are not the whole of the science of politics any more than the requirements and logical limits of the general security are the whole of the science of criminology.

Casting off of the past is not the whole of progress. Institutional waste, the needless destruction of the old in introducing the new, has always to be guarded against. It would be nothing less than institutional waste to throw away the idea of a profession in order to develop services to be performed by government that politically organized society in the last century made no attempt to provide. A reasonable development of the service state does not require such things as the teachers' strikes we are beginning to see, much less the physicians' or

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With the preoperative diagnosis of "pseudomyxoma peritonei" an exploratory laparotomy was performed. From 6 to 7 liters of gelatinous, yellowish-gray, translucent material was found in the abdominal cavity. Firm, yellow-gray, opaque formations, smooth on the surfaces and measuring 0.2 to 1 cm across, were seen floating in this gelatinous material, which had a golden sheen throughout. As it was impossible to remove all this material by suction, it had to be scooped out by hand and by sponging. Both visceral and parietal peritoneum were studded with firmly adherent, tiny, whitish, seed-like growths, approximately 1 or 2 mm in diameter, which could not be whisked off. The left ovary was identified and found to be normal (the right ovary had previously been removed). The liver could be inspected and was essentially normal except that its undersurface was bound tightly down with adhesions to the transverse colon and omentum. Attached to the right and middle portion of the transverse colon was a multiloculated cystic mass, which apparently lay in the gastrosplenic omentum. The walls of the mass were not intact and showed several openings; they were thin and limp in places, and firm and calcified in others. The patient's condition at this time did not permit any attempt to remove the cystic mass, and the abdomen was closed.

Pathological examination of the pieces of tissue from the cystic mass and from a few peritoneal implants showed them to be composed of an interlacing of connective-tissue fibers and cells in the meshes of which lay structureless basophilic

cium 98 mg, and the phosphorus 2.8 mg per 100 cc. The acid phosphatase was 3.2 King-Armstrong units, and the alkaline phosphatase 2.9 Bodansky units per 100 cc. Occult blood in the feces was shown by the guaiac test. The blood Hinton test was negative.

Seven days after admission a laparotomy was performed. When the abdominal cavity was opened it was found to be filled with gelatinous material that had the same characteristics of that evacuated 1 year before. After removal of this material a multilocular cystic mass was found to surround the hepatic flexure of the colon. The pericolic cystic mass together with the ascending colon and right third of the transverse colon, was resected, and an end-to-end ileocolostomy done with a complementary Weitzel type of catheter ileostomy in the ileum.

Still running a low-grade fever the patient was discharged home for convalescence on the 30th postoperative day.

Pathological examination of the pericolic cystic mass showed it to display a horseshoe shape, one branch of which

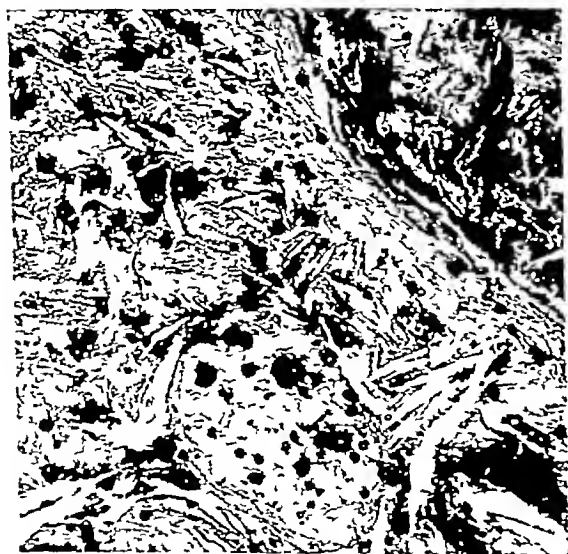


FIGURE 1 Cholesterol Crystals and Lime-Salt Deposits in the Gelatinous Exudate within the Abdominal Cavity

material. Mesothelial cells and foreign-body giant cells could be recognized here and there, being especially numerous around cholesterol crystals. No mucus-secreting epithelial cells could be identified. Bacteriologic examination of the intra-abdominal gelatinous exudate failed to reveal the presence of micro-organisms; tubercle bacilli included.

Six months after operation the abdomen began to swell again and when the patient was readmitted, 1 year later, it measured 40 inches in diameter at the level of the umbilicus in the recumbent position; a fluid wave was clearly elicited.

Examination of the blood disclosed a red-cell count of 4,050,000, with a hemoglobin of 15.5 gm per 100 cc., and a white-cell count of 10,450, with a normal differential. Urinalysis showed a specific gravity of 1.005 to 1.015, and albumin from 0 to 110 mg, in different specimens. The sediment was not remarkable except for occasional white and red blood cells. The blood sugar was 80 mg, the nonprotein nitrogen 34 mg, the blood chloride 608 mg, the cholesterol 175 mg, the amylase 13.5 mg, the diastase 33 units, the cal-



FIGURE 2 Inflammatory Reaction at the Site of Crystallized Cholesterol Deposits

measured 12 by 7 by 6 cm and the other 14 by 8 by 7 cm. Both externally and on the cut section the mass consisted of poorly defined, intercommunicating cystic spaces from 0.5 to 2 cm across. Some of the cystic spaces were empty, whereas others contained a gelatinous, yellow-gray material imbedded in which bits of chalk-like, whitish debris were noticeable.

The walls of the cyst, upon microscopical examination appeared to be composed of loosely packed connective-tissue fibers, poor in cells in some areas and rich in cells, mostly fibroblasts, in others. Islands of necrotic fat tissue were noticeable here and there, with disappearance of nuclei and replacement of normal structures by an amorphous basophilic material. Escaped fat globules of different sizes and shapes were noticeable throughout. There was concomitant inflammatory reaction, including granulocytic cell infiltration and proliferation of mononuclear phagocytes. Cholesterol crystals and foam cells were a prominent feature, and giant cells of the foreign-body type were noticeable here and there (Fig. 2). The great majority of the cystic spaces failed to reveal any cellular lining and only occasionally a few regularly aligned tall columnar epithelial cells of the secretory type could be seen (Fig. 3). These cells compared exactly to the lining epithelial cells of the ovarian cyst removed 9 years before (Fig. 4), and no mitotic figures or any other finding pointing to cancerous degeneration could be recognized.

Microscopical examination of the intra-abdominal gelatinous globules showed them to be composed of an outer

The further course of the process depends upon the intrinsic nature and the potentialities of growth of the seeded cells. Cases have been reported in which the process spontaneously regressed through slow reabsorption of the extravasated material. In other cases a peritoneal reaction was found set up around the transplanted mucus and the quiescent epithelial cells, as an attempt, on the part of the organism, to wall off or to engulf the foreign material. Under the same indefinite heading of "pseudomyxoma peritonei" other cases are encountered of true infiltrating cancerous growths, with active proliferation and further dissemination of secreting epithelial cells implanting themselves in the peritoneal surfaces and invading the lymph channels.⁷⁻⁸

The precancerous nature of the mucous membrane of the appendiceal mucocele has been emphasized by Waugh and Findley,⁹ Hentz¹⁰ and Oberndorfer¹¹ have pointed out that a cancerous degeneration may take place in the secretory epithelial cells, poured into the abdominal cavity. According to Woodruff and McDonald¹² there are two kinds of mucocele one, which is underlined by cancerous degeneration of the glandular epithelium, is more apt to lead to the development of pseudomyxoma peritonei, the other, on the contrary, is due to simple obstruction of the appendiceal lumen, retention of secretion and mural dilatation, and it is less likely to give rise to this abdominal complication.

There are recorded cases of pseudomyxoma peritonei developing as late as seventeen years after removal of the original ovarian cyst.¹³ As in the case reported below, the seeded epithelial cells can remain quiescent for many years, still preserving their potentialities of growth and secretion.

It is not within the purpose of this study to enter into the discussion of the mucinous or pseudomucinous nature of the exuded material. An elementary differentiation of mucin and pseudomucin is based on the property of the former to be precipitated by acetic acid. Pseudomucin is said to be alkaline in reaction, and mucin, acidic, hence the former assumes the acid dyes, and the latter the basic dyes. Accordingly, some authors have considered the inner kernel of the gelatinous globule to be a pseudomucin that stains red with eosin, and the outer layer to be a mucin that takes the basic hematoxylin dye. Based on these distinctive characteristics is the conclusion of Fraenkel² and Hughes¹⁴ that the intraperitoneal gelatinous exudate, in connection with ovarian cysts, is a pseudomucin that resulting from a ruptured mucocele is regarded as a mucin. If this could be accepted, the ability to determine the mucinous or pseudomucinous nature of the peritoneal content would be of significant diagnostic value in the cases in which the origin of the process is not clear, but this possibility is disproved by existing data. In 6 of the 142 mucoceles of the appendix examined by Dodge¹⁵ in which the contents were examined, the material appeared to be

a mucin in 3, a pseudomucin in 2 and a colloidal suspension in 1. Phemister¹⁶ also found the secretion obtained from an appendiceal gelatinous cyst to be a pseudomucin. As for the mucinous or pseudomucinous nature of the secretion of the cystic ovarian tumors, the predominant opinion favors Schiller's¹⁷ conclusion that any distinction between the two is not justified, the colloidal phase of the matter being responsible for the differences encountered from case to case.

New aspects in the controversial subject of pseudomyxoma peritonei are offered by the case presented below, inasmuch as it shows that a cholesterol phanerosis can occur in the intra-abdominal gelatinous exudate and that the seeded secreting cells can remain quiescent for many years, still preserving their potentialities of growth and function. As far as we know there are no preceding cases in the literature illustrating the coexistence of a cholesterous and mucinoid effusion.

CASE REPORT

A 75-year-old woman was first admitted to this hospital on March 16, 1947, with the chief complaint of abdominal pain and loss of weight.

Nine years previously a twisted right ovarian cyst of the "pseudomucinous" type had been removed at another hospital. At that time the appendix was also removed and found to be normal. After this operation the patient felt well for about 3 years and then began to suffer from upper abdominal distress, which was attributed to a diaphragmatic hernia. For the past 2 years the appetite had been poor, and she had lost 30 pounds in weight. She had always been constipated, but no bloody, tarry or acholic stools had been noticed at any time. For the past 2 months she had begun to notice a sharp, nonradiating painful sensation in the right lower abdomen, which occurred every week or so and lasted 10 to 15 minutes.

Physical examination revealed a chronically ill, elderly woman. The abdomen was distended, with a shifting dullness, and a fluid wave could be elicited. The liver edge was not felt, and no abnormal masses could be palpated in the abdominal cavity.

The temperature, pulse and respirations were within normal limits. The blood pressure was 165 systolic, 75 diastolic.

Examination of the blood showed a red-cell count of 3,250,000, with a hemoglobin of 10.5 gm per 100 cc., and a white-cell count of 7000, with 72 per cent neutrophils, 24 per cent lymphocytes, 1 per cent monocytes and 3 per cent eosinophils. Urinalysis was insignificant except for a persistent low specific gravity (1.007 to 1.010). The blood sugar was 87 mg., the nonprotein nitrogen 20 mg., and the total protein 6 gm. per 100 cc., the blood amylase was 12 units per 100 cc. Occult blood in the stools was shown on several occasions by a guaiac test. The cephalin-flocculation and blood Hinton tests were negative.

X-ray studies revealed a congenital shortening of the esophagus, with herniation of about half the stomach into the thorax, through the esophageal orifice of the diaphragm. A large, lobulated, ring-like area of calcific density was noticeable in the right middle portion of the abdomen anteriorly. This shadow was believed to be consistent with the presence of a calcified mesenteric cyst or similar type of intrinsic abdominal mass.

A peritoneoscopy was performed, but owing to the presence of an enormous quantity of gray-yellow gelatinous material in the abdominal cavity none of the organs or the peritoneal surfaces could be clearly visualized.

Pathological examination of a few nubbins of yellowish, firm tissue obtained at peritoneoscopy, showed a structureless basophilic material imbedded in which lay abundant cholesterol crystals and lime-salt deposits (Fig. 1).

several years previously had had an operation for empyema

The etiology of the process is not clear. In about 50 per cent of the cases pulmonary tuberculosis co-existed.²¹ Diabetes or syphilis or a combination of these with tuberculosis has sometimes been considered a causal factor. Even though tubercle bacilli could not be demonstrated in many cases Erwin²⁰ has expressed the opinion that by virtue of chronicity, tuberculosis is the disorder most calculated to evoke such cholesterosis and that there is a reason to suspect a tuberculous basis in most of the published cases of cholesterous pleural effusion.

Protracted exudation, tendency to sequestration of the exudate, progressive thickening of the enclosing membrane and consequent delay in the normal process of reabsorption provide the pleural space with the conditions most favorable for the development of the process. It is not, however, the only location in which cholesterol crystallization has been recorded in association with an exudative process. Bignami²² has found a comparable situation in a case of hydrocele (cholesterinic hydrocele), Fabris²⁴ in a case of pyonephrosis (cholesterinic pyonephrosis), and Lugo²⁵ within a cyst in the subdural space. Effusions of cardiac and renal origin are, in general, terminal complications of the underlying disease. Therefore, they seldom provide the conditions necessary to cholesterol deposition, nevertheless a few cases exemplifying this possibility have been reported.

Regardless of the location, the genetic mechanism of the process is apt to be the same in all cases. As for the source of the cholesterol in the exudate, a number of investigators have suggested a hematic origin.²⁰ Against this as the only source is the normality of cholesterol blood levels in the great majority of the reported cases (our own included), the higher cholesterol content of the exudate as compared to that of the blood itself and the fact that the progressive thickening of the enclosing membranes obviously embarrasses any interchange between the constituents of the circulating body fluids and the constituents of the exudate. This has been proved by an experiment by Bever²⁶. He added sodium salicylate to the pleural space of patients with cholesterinic pleurisy and noticed a marked slowing down in the urinary elimination of the introduced substance as compared to that occurring after injection of the same chemical in a simple serous pleurisy.

The possibility of a synthetic origin of the cholesterol from the exudate itself has been suggested by Barbier and Tricaud,²⁷⁻²⁸ who noticed increase of the cholesterinic content in the fluid extracted from a patient with cholesterol pleurisy, but this has not been confirmed.²⁶ A participation of the corpusculated elements of the exudate in the formation of the cholesterol in the presence of proteolytic enzymes splitting the ¹¹⁻¹² proteins has also been consid-

ered. The amount of cholesterol contributed in this fashion is not sufficient, however, to account for the high cholesterinic content of the exudate. There are in addition, recorded cases in which no cellularity was demonstrable in the exudate.

The tendency of the necrotic tissues to draw lime salts and neutral fats is well known, it might not be surprising, therefore, that the damaged tissues themselves enclosing the exudate would provide the conditions necessary to attract the cholesterol circulating in the body fluids and to provide additional cholesterol through the desquamation and melting in the exudate of degenerated cellular elements.

It is most likely that the cholesterol in the exudate derives from different sources including the blood stream, the corpusculated elements in the exudate and the membrane enclosing the exudate itself, each of these various sources or a combination of them playing the main role in the different cases. This conclusion also applies to the case reported above.

As for the conditions leading to the crystallization of the cholesterol in the exudate, it has been thought that the phenomenon is related to a rupture of the chemical physical balance of the constituents and that whenever the cholesterol reaches a critical concentration, crystallization occurs. Against this view is the absence of any quantitative relation between the free or combined cholesterinic fraction and the fraction of crystallized cholesterol.

Desbordes and Levy²⁹⁻³⁰ have shown that as effusions in the body cavities become old the total protein remains constant but an inversion occurs in the albumin-globulin ratio, and this is accompanied by a decrease of the cholesterolytic power of the fluid. This observation is in agreement with the results of the experiments of Mauriac³¹ showing inversion of the albumin-globulin ratio to the advantage of the globulins without notable lowering of proteins, in rabbits with induced hypercholesteremia. It seems, therefore, that a part of the cholesterol exists in the state of a "complex" associated with the albumin-globulin combination, this liaison being apparently related to the globulin and the albumin contributing to the holding in solution of the cholesterol.

All this has been advocated by Erwin²⁰ to explain the presence of crystallized cholesterol in his case of pleural effusion "as the fluid ages the globulin increases, the albumin decreases and a cholesterol phanerosis develops in the form of crystals giving the golden-sheen observed in several of the reported cases."

The same explanation can be advanced for the case reported above. Protracted exudation and progressive thickening of the enclosing membranes provided the ideal conditions to prevent the reabsorption of the exuded material and the interchange of constituents with the constituents of the circulating body fluids, hence the disruption in the albumin-

basophilic staining laminated hull and of an eosinophilic center, which consisted of finely granular material with occasional cholesterol crystals

Chemical analysis of the abdominal fluid, 8 liters in amount, was performed. A trace of nucleoproteins was obtained by

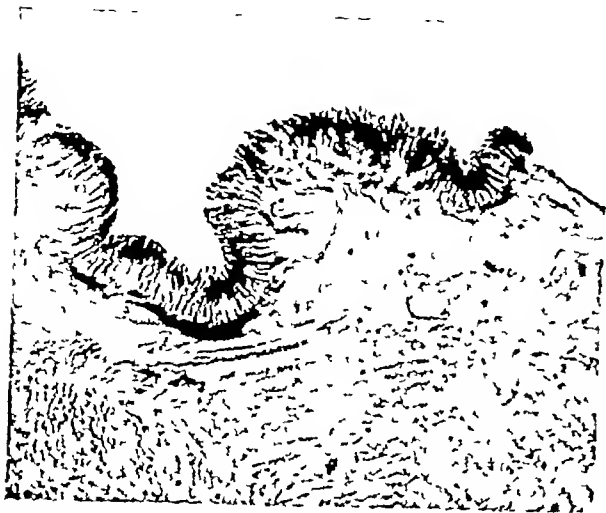


FIGURE 3 Regularly Aligned Secretory Epithelium in a Peritoneal Implant, Exactly Reproducing That Seen in Figure 4

the acetic acid test, as well as by the Almen reagent, after heat treatment of the fluid to remove coagulated protein. However, a qualitative test for phosphorus on the coagulated protein was positive, indicating possibly that some of the nucleoproteins had been precipitated by heating to 100°C. The fluid had a total cholesterol of 229 mg, total phospho-

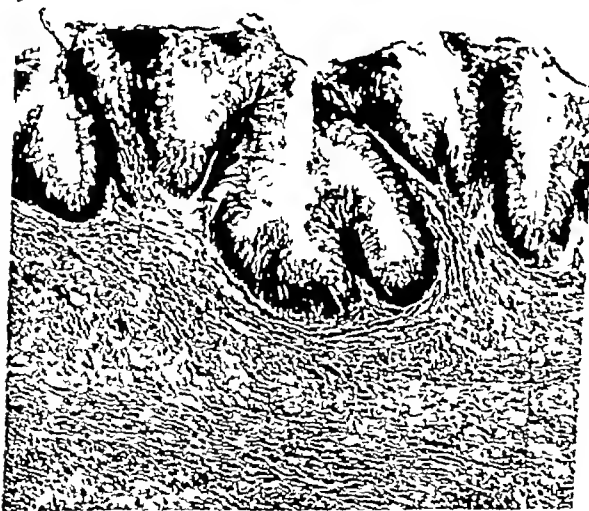


FIGURE 4 Pseudomucinous Cyst Removed Nine Years before Admission

lipids of 62.5 mg, total lipoid fatty acids of 134 mg and neutral fat of 27 mg per 100 cc.

Bacteriologic examination revealed *Escherichia coli*.

The peritoneal cavities of 2 guinea pigs and 6 white mice were injected with 0.5 and 0.3 cc, respectively, of an emulsion of the abdominal exudate. All the animals remained healthy, and when they were killed, from 2 to 4 months after inoculation, no traces of the injected material or any visible tissue reaction could be found.

DISCUSSION

In the case reported above as in many comparable cases in the literature, the origin of the gelatinous exudate in the peritoneal cavity could be traced to a "pseudomucinous" ovarian cyst.

Nine years occurred between the removal of the ovarian cyst and the second operation. This shows that the seeded epithelial cells can remain quiescent for many years, still preserving their potentialities of growth and function.

To judge from the amazing amount of accumulated secretion evacuated from the abdominal cavity when the condition was first detected (from 6 to 7 liters) and by the promptness with which the abdomen filled up again within the year, with an additional 8 liters of similar material, one would have expected to find extensive seeding of secreting epithelial cells in the peritoneal surfaces. Instead, no secretory epithelium could be detected in the pieces of tissue removed at exploratory laparotomy, and only after many blocks of tissue had been cut through were a few cells with these characteristics seen in the removed pericolic cystic mass.

The failure to reproduce the condition in mice and guinea pigs after intraperitoneal inoculation of particles of the exudate is perhaps best explained on the basis of the paucity of secreting epithelium. A singular aspect was the presence of huge amounts of cholesterol crystals in the peritoneal exudate and in the enclosing peritoneal membranes.

Cholesterous effusions have been described in a variety of conditions, but except for a short account in the paper of Probst and Lassar¹⁸ on cholesterol crystal inclusions within the gelatinous globules in a case of appendiceal myxoglobulosis, no mention could be found of a similar condition in any of the reported cases of pseudomyxoma peritonei.

Churton,¹⁹ in 1892, is credited with the first description of a chronic pleural effusion characterized by the presence of cholesterol crystals. In 1941 Erwin²⁰ found 30 similar cases recorded, and since then only a case by Evander²¹ has been added to this meager series. In practically all reported cases there was a history of long-standing effusion, showing little tendency to spontaneous reabsorption and repeatedly recurring after evacuation. The fluid, as a rule alkaline in reaction, was variously described as clear or turbid, with a color ranging from light yellow or brown to dark red. In some cases a few inflammatory cells, or fragments of cells, were seen. In others several hundred cells were present. The fluid was usually encysted by firm, fibrous bands, and the pleural surfaces were greatly thickened. In all cases the recognition of the process depended entirely upon the accidental discovery of the polyhedral cholesterol crystals in the absence of clinical symptoms or signs that might have made one aware or suspicious of the existing condition. Nearly all patients were middle-aged men, only a report by Sharpe²² deals with a nine-year-old who

several years previously had had an operation for empyema

The etiology of the process is not clear. In about 50 per cent of the cases pulmonary tuberculosis co-existed.²¹ Diabetes or syphilis or a combination of these with tuberculosis has sometimes been considered a causal factor. Even though tubercle bacilli could not be demonstrated in many cases Erwin²⁰ has expressed the opinion that by virtue of chronicity, tuberculosis is the disorder most calculated to evoke such cholesterosis and that there is a reason to suspect a tuberculous basis in most of the published cases of cholesterous pleural effusion.

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globulin liaison, which normally contributes to the holding in solution of the cholesterol, followed by its precipitation and formation of the characteristic rhomboidal crystals

SUMMARY

A case of "pseudomyxoma peritonei," most unusual for the presence of large deposits of cholesterol crystals in the exudate, is presented. Protracted exudation and progressive thickening of the enclosing membranes, interfering on one side with the reabsorption of the exuded matter and on the other with the interchange of its constituents with the constituents of the circulating body fluids, are advanced to explain this cholesterol phanerosis. The origin of the process could be traced to a "pseudomucinous" cystadenoma of the ovary removed nine years before. The long period intercurring between the removal of the cyst and the development of the abdominal condition shows that the seeded epithelial cells can remain quiescent for many years, still preserving their potentialities of growth and function.

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VENTRICULAR STRAIN AND VENTRICULAR HYPERTROPHY*

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WHEN medical terminology was less precise the expression "strained heart" was employed at times to describe obscurely but ominously diseased hearts. This diagnosis is no longer made, but currently the terms heart strain and ventricular strain are occasionally used to identify electrocardiographic patterns encountered in various types of heart disease.¹ The dictionary defines strain as "the hurt or injury from excessive tension or use, as of muscles, nerves and organs, deformation or distortion due to stress or force, stretched beyond its proper limits." Stress is "the force, pressure or influence impinging upon or acting against the member or organ under consideration."

The heart is normally subjected to stresses against which it operates to perform its work. In the absence of myocardial disease these are adequately countered without injury or strain. Furthermore, the reserve capacity of the normal heart enables it to cope successfully with greatly increased stresses as during excitement, violent exercise, anemia, pregnancy and infection. In a like manner, patients with moderate hypertension, valvular insufficiency or chronic pulmonary disease may go for many years without any evidence or symptoms of cardiac involvement. However, if the stresses exceed physiologic reserves, strain occurs, which may be acute, as in pulmonary embolism, or chronic, as in important hypertension. These become objectively manifest as dilatation and, if the condition is chronic, dilatation and hypertrophy (distortion). This stage may or may not be accompanied by symptoms. Strain may occur with an essentially normal myocardium. On the other hand, disease of heart muscle renders the heart less capable of coping with normal physiologic stresses. In either event strain represents a state of imbalance. It should be apparent that although it is usually the result of organic disease, heart strain is actually a functional disorder that is often reversible.

Although the term heart strain should not properly be applied to an electromechanical tracing, specific electrocardiographic patterns are encountered either as the result of or occurring coincident with the cardiac "hurt or injury" of ventricular strain. The exact cause for the observed abnormalities is obscure. They may somehow be related to mechanical stretching or distortion of the myocardium or to more subtle alteration of the metabolic processes. In either event they are limited almost wholly to the

repolarization process and result in depressions of the ST segment and T-wave inversions.

In 1935 the electrocardiographic findings in acute pulmonary embolizations were described.² These consisted of the development of an S wave in Lead I and a Q wave in Lead 3 and of deviations in the ST segments in Lead I and 3. There were also T-wave inversions in L_{III} and L_{IV} . Later studies indicated that the S wave in Lead I and Q wave in Lead 3 were manifestations of cardiac rotation and not of myocardial distress. Clockwise rotation of the heart on its long axis was also observed as shown by development of S waves in the leads from the left side of the chest. Inversion of the precordial T waves was, apparently, the only valid evidence of heart strain and was limited to leads obtained over or derived from the right ventricle. In some cases of chronic cor pulmonale resulting from persistent pulmonary hypertension, considerable right ventricular hypertrophy occurs, and in addition to the electrocardiographic findings noted in the acute form the R waves in the right precordial leads become prominent and the S waves small.^{3,5}

It is apparent, therefore, that uncomplicated strain of the right ventricle results in ST-segment and T-wave changes in the leads from the right precordium, whereas right ventricular hypertrophy produces alterations in the QRS complexes. For the sake of completeness it is well to note that other electrocardiographic forms are encountered in right ventricular disease. For example, the electrocardiogram may be entirely normal in both acute and chronic cor pulmonale. Chronic strain of the right side of the heart with moderate hypertrophy may result in an electrocardiographic pattern that is indistinguishable from acute strain, and both resemble the findings commonly seen in children and in some adult Negroes. Partial or complete right-bundle-branch block is sometimes found in both acute and chronic cor pulmonale but appears also in coronary-artery disease.

Investigators are in agreement regarding the electrocardiographic criteria that may be used to distinguish right ventricular strain (Fig 1) from right ventricular hypertrophy (Fig 2). The agreement is not quite complete, however, with left ventricular disease. The term left "heart strain" has now been largely replaced by "hypertrophy." This may be because "strain" has obscure implications whereas "hypertrophy" is obvious and can be co-ordinated with physical, x-ray and autopsy findings. Furthermore regardless of its exact meaning, strain of the left ventricle is almost always accompanied by hypertrophy.

*From the Medical Service, Veterans Administration Hospital. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions or conclusions drawn by the author.

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From an electrocardiographic point of view, there is, unfortunately, no clinical state involving the systemic circulation quite comparable to that which obtains in the lesser system after extensive pulmonary embolization. A somewhat similar situation might arise during the hypertensive crisis of pheochromocytoma. However, few striking electrocardiographic changes are encountered here, possibly because the left ventricle is better able to handle acute insults than the right. Nevertheless, it appears probable that strain of the left ventricle occurs in other situations and that it results in a distinguishable electrocardiographic picture.

The pattern of left ventricular hypertrophy has recently been reviewed and more carefully defined.^{3,4,6} It is considered to be present when the QRS complexes from the left side of the precordium (V_1 or V_4 or both) consist largely or entirely of R waves of unusual height and duration (greater than 27 mm in height, with intrinsic deflection of 0.04 second or more after the origin) or when the sum of S in V_1 and R_1 exceeds 35 mm (See Fig 6). Commonly, these changes are also accompanied by a depressed or sloping ST segment and an inverted T wave in Lead V_1 or V_4 (See Fig 7). Usually, the heart is horizontal, but the same changes may occur with the heart in the intermediate or even in the

may be reversible. As a corollary it is likely that the second indicates hypertrophy without coincident strain.

In support of these contentions a series of clinical situations is submitted for consideration. In some of these, electrocardiographic patterns similar to hypertrophy (ST-segment and T-wave changes but R waves of ordinary amplitude) were observed to develop acutely or to disappear. The time consumed was brief, and there were no measurable differences in heart size. In another group of pa-

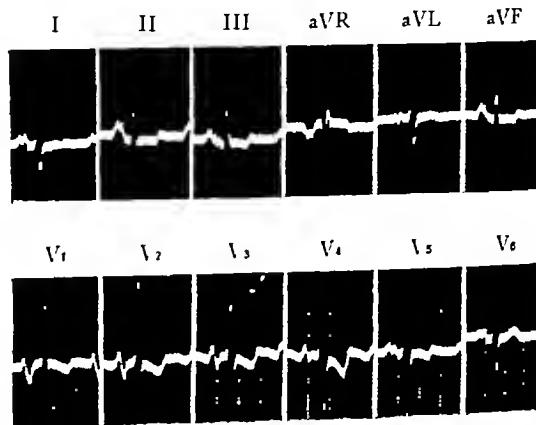


FIGURE 2 Right Ventricular Hypertrophy in a Thirty-Two-Year-Old Man with Mitral Stenosis

Note the prominent R, small S and inverted T waves in Lead I, I₂ and I₃, with deep S and upright T waves in I₄. Large or biphasic P waves, or both, are the result of auricular hypertrophy.

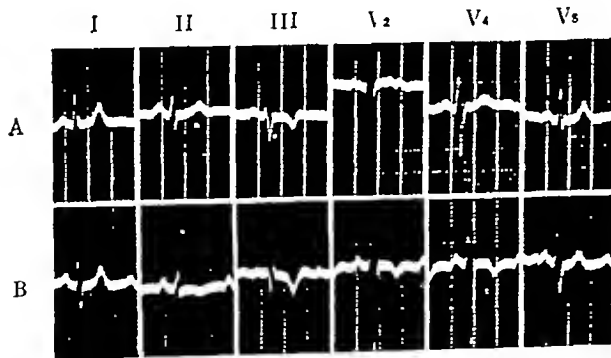


FIGURE 1 Right Ventricular Strain in a Forty-Seven-Year-Old Man with Pulmonary Fibrosis

A=record taken early in the disease B=record taken five months later. Note the development of S wave in Lead I and Q wave in Lead 3 and inversion of the T waves in Lead 2 and 3, as well as the deepening of S waves in I₄ and I₅, with inversion of the T wave in V₂ and V₄.

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A left hypertrophy-like pattern has been observed in patients with hypertension or aortic-valve disease and congestive failure upon recovery of compensation. Occasionally, patients in congestive (right ventricular) failure secondary to left failure resulting from hypertension or aortic-valve disease demonstrate normal electrocardiograms. However, upon recovery electrocardiographic findings resembling left ventricular hypertrophy become apparent in days to weeks. The following case is used to illustrate this phenomenon.

CASE 1 A 69-year-old former laborer, with a past history including hypertension, thrombophlebitis and pulmonary embolism, was admitted to the hospital because of weakness and evidence of myocardial failure. There was extensive cerebral arteriosclerosis and senility. Physical examination revealed a heart that was at the outer limits of normal in size (confirmed by x-ray study), pulmonary moisture and extensive edema of the legs and thighs. The blood pressure was 180/110. The electrocardiogram on admission was essentially normal (Fig 3A). He responded well to treatment of his

cardiac failure with clearing of both the pulmonary and peripheral edema. At this time the electrocardiogram developed findings resembling those of left ventricular hypertrophy with ST-segment and T-wave changes but R waves of normal amplitude (Fig 3B). In spite of cardiac improve-

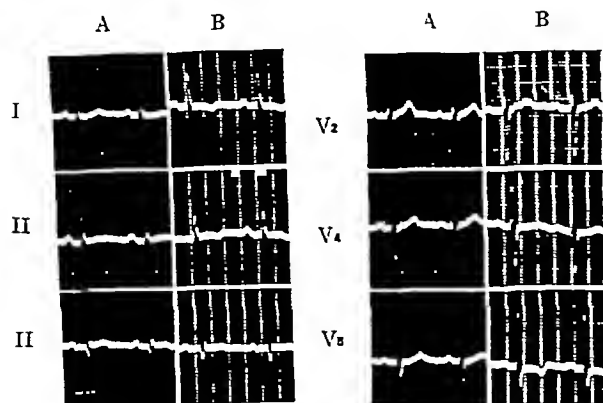


FIGURE 3 Electrocardiograms in Case 1

During congestive failure the record is essentially normal (A). Upon recovery from failure (B) there are sloping ST segments and inverted T waves in Lead I, 2 and 3. The size of the QRS complexes is unchanged and within normal limits. This is the pattern of left ventricular strain.

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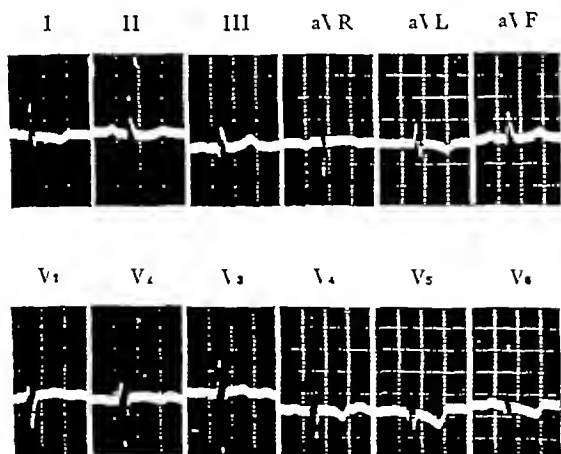


FIGURE 4 The Pattern of Left Ventricular Strain without Hypertrophy (Case 2)

Note the sloping ST segments and inverted T waves in Lead I and aVL and in the left precordial leads. The QRS complexes are of normal amplitude.

able frequency in patients with angina pectoris but no hypertension, hypertrophy or valvular disease. The following case illustrates this situation.

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HYPERTROPHY-LIKE PATTERN IN ANGINA DECUBITUS

The development of an electrocardiographic pattern resembling that of left hypertrophy during the course of angina decubitus is a rarely encountered phenomenon that may be found in the absence of hypertrophy, hypertension and so forth. It may

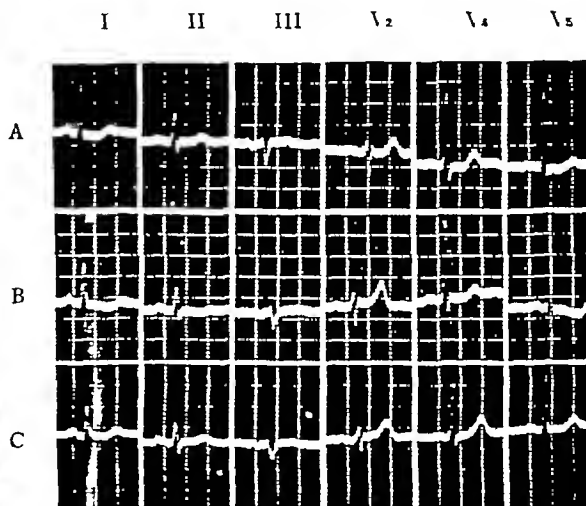


FIGURE 5 Electrocardiograms in Case 3

On admission the record is normal except for evidence of digitalis (A). Five days later during a period of angina decubitus, there are sloping ST segments and inverted T waves in Lead I, 2 and 3 (B). Three months later, the electrocardiogram is within normal limits (C).

occur in a few days and has been noted to disappear together with improvement in the clinical state.

The following case is typical of those in this group.

CASE 3 A 56-year-old government employee had been aware of retrosternal pain on effort for 3½ years. This gradually increased in frequency and severity, and 3 weeks before admission the patient could walk only 1 block without pain. Two days prior to entry pain began to occur at rest and became almost continuous. This was barely relieved by nitroglycerin and digitalis supplied by his family physician. The patient was an obese white man who showed the slightest possible trace of ankle edema. However, there was no dyspnea or orthopnea. On x-ray examination the heart was just within normal limits of size. The transverse diameter of the heart was 15 cm, and the internal diameter of the chest was 31 cm. The heart was in the horizontal position. It was narrow waisted and of normal area. The blood pressure was 152/92.

From an electrocardiographic point of view, there is, unfortunately, no clinical state involving the systemic circulation quite comparable to that which obtains in the lesser system after extensive pulmonary embolization. A somewhat similar situation might arise during the hypertensive crisis of pheochromocytoma. However, few striking electrocardiographic changes are encountered here, possibly because the left ventricle is better able to handle acute insults than the right. Nevertheless, it appears probable that strain of the left ventricle occurs in other situations and that it results in a distinguishable electrocardiographic picture.

The pattern of left ventricular hypertrophy has recently been reviewed and more carefully defined.^{3,4,6} It is considered to be present when the QRS complexes from the left side of the precordium (V_1 or V_6 or both) consist largely or entirely of R waves of unusual height and duration (greater than 27 mm in height, with intrinsic deflection of 0.04 second or more after the origin) or when the sum of S in V_1 and R_6 exceeds 35 mm (See Fig 6). Commonly, these changes are also accompanied by a depressed or sloping ST segment and an inverted T wave in Lead V_1 or V_6 (See Fig 7). Usually, the heart is horizontal, but the same changes may occur with the heart in the intermediate or even in the

may be reversible. As a corollary it is likely that the second indicates hypertrophy without coincident strain.

In support of these contentions a series of clinical situations is submitted for consideration. In some of these, electrocardiographic patterns similar to hypertrophy (ST-segment and T-wave changes but R waves of ordinary amplitude) were observed to develop acutely or to disappear. The time consumed was brief, and there were no measurable differences in heart size. In another group of pa-

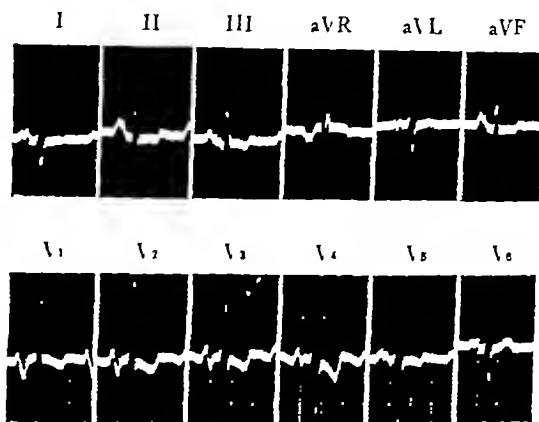


FIGURE 2 Right Ventricular Hypertrophy in a Thirty-Two-Year-Old Man with Mitral Stenosis

Note the prominent R, small S and inverted T waves in Lead I, II and III, with deep S and upright T waves in V_4 . Large or biphasic P waves, or both, are the result of auricular hypertrophy.

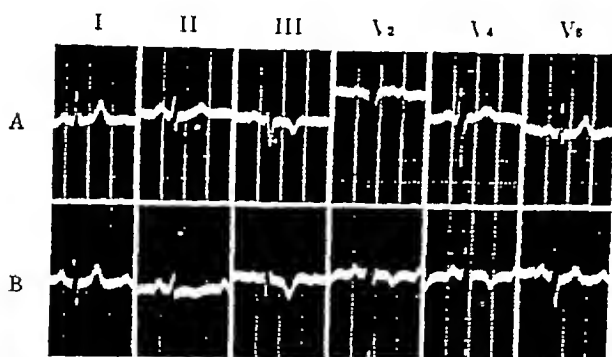


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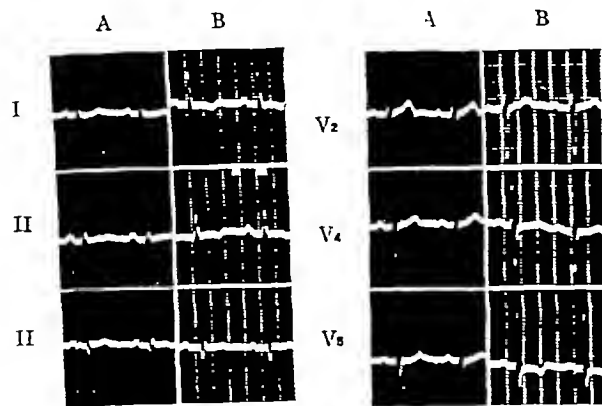


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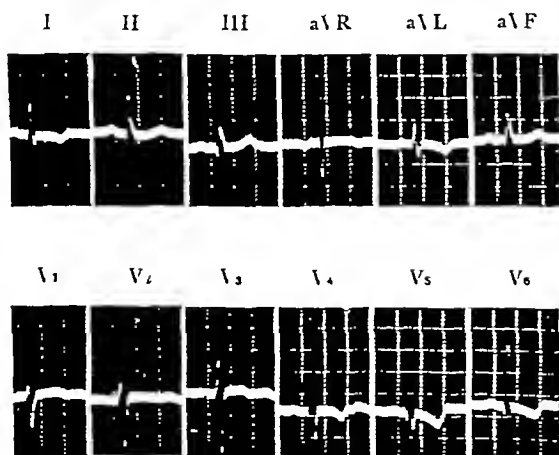


FIGURE 4 The Pattern of Left Ventricular Strain without Hypertrophy (Case 2)

Note the sloping ST segments and inverted T waves in Lead I and aVL and in the left precordial leads. The QRS complexes are of normal amplitude.

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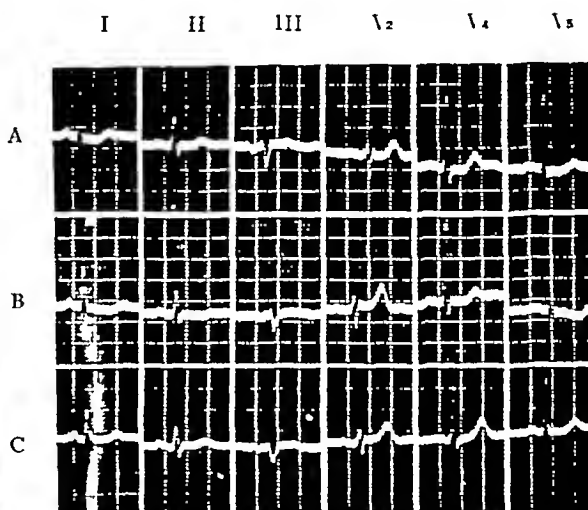


FIGURE 5 Electrocardiograms in Case 3

On admission the record is normal except for evidence of digitalis (A). Five days later during a period of angina decubitus, there are sloping ST segments and inverted T waves in Lead I, II and III (B). Three months later, the electrocardiogram is within normal limits (C).

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on admission and dropped to 130/80 shortly thereafter. During the 1st week the patient had 20 to 30 attacks of angina each day while confined to bed, but the frequency gradually decreased until by the 7th week he was entirely free of pain. He was discharged after 9 weeks in the hospital. The electrocardiogram on admission showed digitalis effect but was not otherwise striking (Fig 5A). Five days later there were sloping ST segments and inverted T waves in leads V_3 and V_4 (Fig

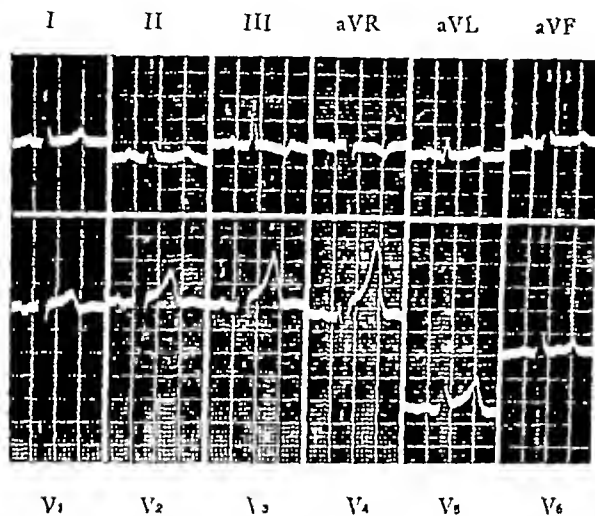


FIGURE 6 Electrocardiograms in a Patient with Hypertension and Cardiac Hypertrophy, Showing Left Ventricular Hypertrophy Without Strain

The limb leads are normal with the heart in the semi-vertical position. There is a huge S wave in Lead I₂ (3.2 mV), and R wave in Lead I₁ (3.9 mV). The T waves are upright in all precordial leads.

5B). Three months after admission, when the patient was essentially free of complaints, the electrocardiogram was again normal (Fig 5C).

DISCUSSION

The cases used above to illustrate the development and recession of an electrocardiographic pattern are obviously unusual. Cardiologists are much more familiar with patients in comparable clinical situations who have not shown similar changes. However, these differences can be reconciled. Generally, patients with sufficient hypertensive disease to result in congestive failure have well marked hypertrophy patterns (Fig 7), which cannot be expected to alter greatly. In a like manner patients with angina decubitus ordinarily have enough coronary-artery disease to result in grossly abnormal electrocardiograms, which ordinarily change only to become worse. One can expect rapid and significant development, therefore, only in the rare cases in which the tracings are still essentially normal but delicately balanced and in which little additional strain is required to precipitate electrocardiographic evidence of this phenomenon.

The following explanation is offered to account for the presence of the electrocardiographic pattern resembling that of left hypertrophy in the clinical states described above.

In the cases of congestive (right ventricular) failure secondary to disease of the left ventricle the presence of a heart-strain pattern prior to decompensation has not been proved. It may or may not have been present. Most observers are in agreement that cardiac output is either absolutely or relatively diminished during such failure. It follows naturally that the work of the left ventricle is proportionately lessened and that the left ventricle is temporarily relieved of its customarily increased stress. Accordingly, the strain of the left side of the heart is similarly partly or completely alleviated, and the electrocardiogram may be normal. Upon recovery of compensation, however, the left ventricular output and work increase, and with these there is electrocardiographic evidence of strain. This sequence of events is reminiscent of a somewhat similar phenomenon observed in patients with angina pectoris who

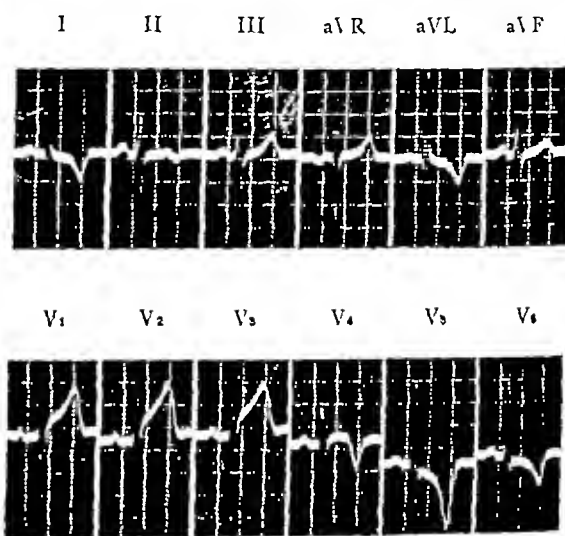


FIGURE 7 Left Ventricular Hypertrophy and Strain in a Patient with Hypertensive Heart Disease and Marked Cardiac Hypertrophy

Note the prominent R waves sloping and bowed ST segments and inverted T waves in Lead I and aVL (RaVL 1.9 mV), deep S wave in Lead I₂ (2.5 mV, trough off record as shown), tall R waves in Lead I₃ (3 mV, peak off record) and depressed, bowed ST segments and inverted T waves in the left precordial leads.

develop congestive failure. Commonly, the angina wanes with the onset of decompensation. It reappears with recovery from failure probably because of the simultaneously increased output and work of the left ventricle.

In angina pectoris the presence of abnormal left ventricular physiology is clear. Here the often extensive coronary-artery insufficiency results in an ischemic and diseased myocardium that is unable to cope with normal stresses (angina decubitus) or moderately increased stresses (angina of effort), and strain ensues.

The frequency of the electrocardiographic pattern of ST-segment and T-wave abnormalities in Lead

V_4 and V_6 in patients with angina but without hypertrophy is too great to be wholly fortuitous. Some cardiologists, in fact, prefer to interpret such findings as "consistent with coronary-artery disease."

In Case 3 described above the strain pattern developed during a period of critical coronary-artery inadequacy. Subsequently, after all pain had disappeared, the electrocardiogram became normal. It is highly improbable that myocardial hypertrophy developed in six days and then disappeared. It is thought that during a period of grave coronary insufficiency the heart was unable to meet its basal physiologic requirements and was strained by normal stresses. This was accompanied by an electrocardiographic pattern thought to indicate left ventricular strain. When an adequate collateral circulation became available the enhanced ability of the heart to perform its work led to both clinical and electrocardiographic improvement. Unfortunately, such close parallels between clinical and electrocardiographic states are rarely encountered.

The pattern of depressed or sloping ST segments and inverted T waves but without abnormally prominent R waves in the outer (left) precordial leads is taken as the electrocardiographic manifestation of left ventricular strain without hypertrophy. This may be reversible. When unusually prominent R waves are also present, hypertrophy and strain coexist. One phenomenon that has not thus far been considered is the lowering of ST segments and T waves resulting from a simple enlargement of the R waves in hypertrophy. Although this is a real influence it presently remains an uncertain and, in any one case, an unmeasurable factor. The ventricular gradient, which is customarily normal in left ventricular hypertrophy, is computed from the limb leads. This discussion primarily concerns the precordial phenomena. These have been shown to differ widely at times from those derived from the limbs. The findings in hypertrophy are ordinarily permanent except when cardiac enlargement can be reduced. This sometimes occurs after sympathectomy in hypertensive patients.

One may, accordingly, conceive of the pattern of left ventricular strain as electrocardiographic evidence of the unphysiologic state that obtains with left ventricular inability to cope with normal or abnormal stresses. In this manner it is possible to account for the occasional appearance of an electrocardiographic picture not grossly dissimilar from that of left hypertrophy in patients without cardiac

enlargement. Such persons generally have coronary-artery insufficiency or intrinsic myocardial disease.

SUMMARY

Ventricular strain is a pathologic state of imbalance that occurs with myocardial inability to contend with normal or abnormal stresses. It may cause reversible electrocardiographic alterations.

Right ventricular strain due to abnormal stress is commonly seen with acutely or chronically elevated pulmonary pressures. Isolated strain of the left side of the heart occurs in coronary-artery inadequacy because of diminished ventricular ability to cope with normal stresses.

Aside from changes due to cardiac rotation, right ventricular strain becomes manifest electrocardiographically by ST-segment and T-wave changes in the right ventricular precordial leads. When significant (probably great) hypertrophy is added, the R waves in the same leads become abnormally tall and broad, whereas the S waves diminish in size.

An electrocardiographic picture superficially resembling that found in left hypertrophy has been observed to develop from apparently normal records in patients with left ventricular disease recovering from congestive failure. It is seen in others who have no cardiac enlargement. The same pattern has also been seen to emerge in patients with rapidly increasing angina pectoris and to clear with clinical improvement.

Observations in these clinical states suggest that distinguishing differences can be noted between strain and hypertrophy of the left ventricle similar to those on the right side.

The ST-segment and T-wave abnormalities in precordial Lead V_4 or V_6 , or both, are considered to be manifestations of left ventricular strain. Enlargement of the R waves in the same leads constitutes evidence of left ventricular hypertrophy. These are usually seen together but may occur separately.

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CONDITIONED-REFLEX TREATMENT OF ALCOHOLISM

I Its Rationale and Technic*

JOSEPH THIMANN, M D †

BOSTON

FEBRUARY, 1949, marked the end of seven years of application of the conditioned reflex as a therapy for alcohol addiction at the Washingtonian Hospital. This fact calls for an evaluation of this part of the total therapeutic plan^{1, 2} concerning chronic alcoholism.

The present article is the first of two dealing with the rationale, technic, indications, contraindications, risks and psychologic aspects of the treatment, as well as its efficacy and methods of evaluating it.

The last two decades have made it quite fashionable for any intelligent lay person, and a veritable shibboleth for a modern professional man, to announce that alcoholism is a disease and that alcoholic patients are sick people. The professional and lay therapist alike consider it necessary to aim at one target—the underlying cause of the patient's addiction. Focusing on this, they analyze the patient for old and recent traumas and try to determine how far these traumas have initiated a discouraging or frustrating mechanism. An attempt, then, at eliminating the neurotic defense mechanisms and building new constructive patterns of life is considered to constitute the treatment of addiction.

Unfortunately, the majority of alcohol addicts continue to relapse even after psychotherapy of one kind or another.

Careful observations of large numbers of patients have confirmed the impression that the psychopathology of alcohol addiction resembles, in certain aspects, that of addiction to narcotics. If a person suffering from gallstones is given morphine for a certain length of time and happens to be predisposed to addiction, the addiction will develop. In such a case it is agreed that removal of the gall bladder will in most cases eliminate the pain, but not the addiction to morphine. By then, the addiction will have developed into an autonomous disease, independent of whether the underlying cause, the gallstone colic, still exists or has been removed. I think that there is reason to assume that the uncontrollable desire for alcoholic beverages is governed by similar laws. It may, of course, be precipitated by an underlying neurosis or some combination of inner and outer factors. From the point at which the addictive pattern has become established, however, it is as autonomous as morphine addiction. From then on the addict does not drink because of his neurosis or whatever has caused his addiction, he does not even drink, as a physician

once put it, "in order to get drunk." He drinks because he is addicted, because the established addiction is self-perpetuating and causes the compulsive need for more and more alcohol. Thus, the impulse for alcohol can best be described as an abnormal conditioned reflex.

If this theory is accepted as a working hypothesis, one will not expect many alcohol addicts to stop drinking after undergoing psychoanalysis or some other psychotherapy without specific treatment for the addiction as such, just as morphine addicts are not expected to give up morphine because the underlying gall-bladder disease and pain have been eliminated. Accepting this hypothesis of the autonomous character of the alcohol compulsion as such does not, of course, mean underrating the importance of psychotherapy in the treatment of the underlying personality disorder, either the primary one, existing in the prealcoholic personality, or the secondary neurosis, which may have developed as a result of the feelings of helplessness, guilt or inferiority incident to the addiction.

The idea of outweighing the craving for alcohol by means of a revulsion established artificially against it is at least as old as Pliny the Elder, who in his *Historiae Naturalis*³ lists quite a few, (somewhat naïve) methods. Beginning in 1930, several European therapists,^{4, 7} among them Dent⁸ in England, reported their experiments in establishing a conditioned reflex against alcoholic impulses.¹ In this country Fleming,⁹ of Boston, seems to have been the first to apply Dent's technic of apomorphine injections to 36 patients, with an estimated success of 35 per cent.

The first reports about highly successful treatment of a large number of alcoholic patients, with subsequent observation over a period of more than four years, emanated from the Shadel Sanitarium in Seattle, Washington,^{10, 12} from 1940 to 1942, an average of 64.3 per cent of total abstinence from alcoholic beverages† among patients treated being claimed. The authors reported the use of a 7.8 per cent solution of emetine, supplemented by pilocarpine and ephedrine as the unconditioned stimulus, the alcoholic beverages constituting the conditioned one. Emetine appeared more appropriate than apomorphine, which was used by Dent, because it caused the desired prolonged nausea and because it lacked the disturbing euphoric and hypnotic after-effects. Several simultaneous exposures to the un-

*These articles represent abstracts from a book that is in the process of being prepared for publication.

†Medical director, Washingtonian Hospital.

‡A recent report from the same institution claims a 44.8 per cent efficacy in an observation period of ten and a half years.¹³

conditioned and conditioned stimuli entailed a reflex association between both. Whether this association developed to the extent of an active and conscious revulsion to and nausea at the sight, taste, smell and even thought of alcoholic beverages, as it usually does shortly after its establishment, or whether it merely developed to the extent of outweighing the compulsive reach for a drink, depends on the technic and — it seems to me — also on the patient's personality. Pavlov already knew that conditioned reflexes are apt to "fade out" if they are exposed for a certain length of time to the conditioned stimulus only, without the reinforcing action of a simultaneous unconditioned stimulus. To prevent the treatment from losing its efficacy, the initial series was followed up by additional sessions (reinforcements), given in intervals during the first year.

Seven years ago, the conditioned-reflex therapy was started at the Washingtonian Hospital.¹⁴ It was modified in technic to increase its efficacy. Furthermore, it was supplemented by methodic psychotherapy and part-time hospitalization,¹⁵ as well as by manipulation of the patient's environment. This included case work with relatives, whenever these measures seemed indicated. Group therapy was organized in the form of semimonthly meetings of the hospital abstinence club comprising all patients who "graduated" from the initial series of the conditioned-reflex therapy. The term "part-time hospitalization" describes an arrangement that combines the advantages of a protective environment with those of the exposure to the unsupervised, normal environment. These patients work full time at their regular place of work, but spend their free time in the hospital. The period of hospitalization is gradually reduced, thus, the patient becomes increasingly able to handle in a mature way all the usual daily problems of an adult.

It may be appropriate to describe here one conditioning session as given at the Washingtonian Hospital.

The treatment room should be arranged in such a way as to eliminate all distracting stimuli.¹⁴ The treatments are given in the morning, because patients react better when fasting and rested. The preliminary medication consists of 10 to 20 mg of Benzedrine sulfate and 1 mg of strychnine sulfate followed by a capsule containing 0.06 to 0.15 gm (60 to 150 mg) of emetine hydrochloride with 1 to 3 glasses of tepid water. Simultaneously, 0.05 to 0.15 gm (50 to 150 mg) of emetine hydrochloride is administered hypodermically. These dosages are easily obtained from a 7.2 per cent solution of emetine supplemented by 1 per cent pilocarpine and 4.8 per cent ephedrine sulfate. Of this solution, 0.6 cc contains 50 mg of emetine, 1 cc contains 75 mg, and 2 cc 150 mg of emetine — the highest single dosage I have ever administered. The percentages in this solution have been arrived at purely

empirically. Experiments with higher concentrated solutions have shown slower or less complete absorption. In other words, 50 mg of emetine in a 13 per cent solution produced a slower and less powerful reaction than the same amount in a 7.2 per cent solution. On the other hand, solutions of less concentration than 7.2 per cent appeared too bulky and therefore uncomfortable.

Immediately prior to the expected emesis the patient is exposed to the sight, smell and taste of the alcoholic beverages that he preferred when on a spell of drinking. The drinks are offered in undiluted form ("straight") and in the usual dilutions ("highballs").

These sessions last twenty to thirty minutes and are repeated daily* for five or six days. They are followed by six or seven preventive one-day treatments, so-called reinforcements, given at intervals ranging from four to twelve weeks. Thus, the application of the initial series together with the reinforcements takes approximately a year. Some patients, anxious to obtain the widest possible margin of safety, ask after the first year of treatment for further reinforcements. Such second-year-treatments have consisted of a series of four reinforcements given at three-month intervals.

I should like to stress the fact that it would be erroneous to assume that this detailed description of the technic enables one to apply it safely and efficiently without an adequate apprenticeship. The reasons for caution are indicated by the great range and variety of the patient's reaction to the conditioned and unconditioned stimuli, innumerable imponderables decisive for the success or failure of the treatment, and the very narrow margin between underdosage and overdosage.

The next article in this series will deal with the physiologic risks of the treatment, indications, contraindications, efficacy and psychotherapeutic aspects.

*Provided no toxic symptoms ensue. Otherwise the sessions were postponed for the necessary length of time. These toxic side effects will be discussed in a later article.

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MEDICAL PROGRESS

RESUSCITATION*

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CARDIORESPIRATORY ARREST

IN THE multitude of clinical and experimental material reported in the last two decades, cardiac arrest and respiratory arrest are usually regarded as two distinct entities. It is true that certain events result in cardiac arrest, whereas other circumstances lead to cessation of respiration, however, because these two are so closely related in pathological physiology and in therapy, thinking on the problems engendered must, in every instance, include both. Synonymous with Courville's¹ phraseology, "respiro-cardiac crises," the term cardiorespiratory arrest is suggested as most appropriate and is used below in referring to this phenomenon.

Cardiorespiratory arrest is one of the most catastrophic events that may occur in medicine and presents the greatest possible emergency. It is characterized by the absence of the two vital functions, circulation and respiration, the patient is apparently dead.

Cardiorespiratory arrest often occurs as an operating-room accident because circumstances of anesthesia and surgery predispose to its development. Of the operating-room accidents in which the arrest occurs as a terminal event in a mortal disease² — for example, in coronary occlusion incidental to an operation, late intestinal obstruction or overwhelming sepsis — this condition may be considered irreversible, and little benefit may be expected from resuscitation. On the other hand, when cardiorespiratory arrest occurs accidentally as a result of factors such as anoxia, drug effect, idiosyncrasy to drugs and abnormal reflex action, there is a

period following the onset of the arrest during which the condition is reversible. Hence, if effective resuscitation is promptly instituted recovery will follow.

The wealth of clinical observation emanating from the operating room in the nature of case reports and discussions, in addition to the knowledge gained from experimental investigations, enables one to form a clearer concept of the problems involved and to place the treatment of this condition — namely, resuscitation, the revival of the apparently dead — on sound physiologic principles.

Cardiorespiratory accidents do not confine themselves to the operating room. In the delivery room, asphyxia of the newborn requires prompt resuscitation therapy, in the home, in industry and elsewhere accidents such as electric shock, drowning, inhalation of foreign material, inhalation of noxious gases, injuries to the chest and poisonings present emergencies in which a knowledge of resuscitation may make the difference between life and death. Therefore, the discussion that follows deals first with this emergency in the operating room, secondly, with the emergency in the delivery room and, finally, with accidents occurring elsewhere.

Pathological Physiology

Anoxia produced by cardiorespiratory arrest. A state of oxygen deficiency occurring in the tissues from whatever cause is designated as hypoxia; continuation of hypoxia to a state of oxygen lack incompatible with life is called anoxia. In the literature, the term anoxia is generally used to designate both hypoxia and anoxia, in the ensuing discussion, this usage of the word is followed.

Many clinical conditions lead to various degrees of anoxia. The most frequent cause is decrease in oxygen supply when oxygen demand is normal.³ Examples are as follows: insufficient oxygen in the atmospheric air (environmental cause) such as high altitude, insufficient intake of oxygen to the al-

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veoli of the lungs (respiratory cause) such as respiratory arrest, respiratory depression, respiratory obstruction, emphysema, asthma, pneumonia, atelectasis and pulmonary fibrosis, inadequate transportation of oxygen from the alveoli of the lungs to the tissues (circulatory cause) such as cardiac arrest, failing circulation, myocardial weakness, valvular disease, pericarditis, arterial spasm and arteriovenous fistula, and depressed tissue activity such as frostbite and edema.

Less frequent causes of anoxia are associated with a normal oxygen supply, but an increased oxygen demand of the tissues (over-utilization anoxia)⁴—for example, exercise, fever, hyperthyroidism and infection. Whereas, the anoxia that develops with the above conditions may be gradual in onset and may be compatible with life for a long time, the anoxia that follows the complete cessation of respiration and circulation in cardiorespiratory arrest is rapidly destructive^{1, 5, 6} to certain vital tissues, especially the brain,⁷ and leads to death in a very short time.

In the human being complete cerebral anoxia for ten seconds produces unconsciousness, that for twenty to thirty seconds causes cessation of electroencephalographic brain waves, and that for three to five minutes produces irreversible pathologic change in the cerebrum.⁵ The medulla with its centers can survive for twenty-five to thirty-five minutes, and the spinal centers from forty to sixty minutes.⁸ The resistance of the brain in very young animals to circulatory arrest is much greater than that of the adult brain.⁹ This may well be the reason why resuscitative efforts have been rewarded with success, most often in young people. Courville's monograph discloses in detail the effect of anoxia on the nervous system, particularly the brain. He found alterations in the cerebral cortex characterized by degeneration of individual cells, patchy areas of necrosis, diffuse zonal necrosis and complete cortical disintegration. Microscopic alterations in the nerve cells explained the ultimate pathological picture encountered, these were sclerotic changes, acute degeneration, ischemic alteration, pigmentary atrophy and ferrugination of nerve cells. More recently, similar studies of post-mortem material have substantially corroborated Courville's findings.^{7, 10} Particularly striking are the degeneration of cerebral and basal-cell ganglions, disappearance of pyramidal cells of the cerebral cortex, increase in astrocytes, proliferation of microglia and severe destruction of the occipital cortex and superior temporal gyrus.

Demonstrable pathological findings caused by anoxia in organs other than the brain are relatively meager. Damage to the myocardium by anoxia⁵ is important because, although it develops less rapidly than that to the brain, it is responsible for the inability of the heart to recover from cardiorespiratory

arrest in cases in which cardiac resuscitation is unsuccessful. Of all tissues, the brain is the most vulnerable and susceptible to oxygen lack.^{1, 5, 6} This explains why in cases in which anoxia has advanced to the point where irreversible changes to the brain have occurred, although life is spared, permanent damage may follow. This can be the case in cardiorespiratory arrest when resuscitation saves life but is not effective enough to prevent permanent brain damage. The patient with permanent brain damage may be a vegetative organism¹¹ who lives on, a burden to himself and to society. In fatal cases, before death supervenes, there may be a period of coma lasting a few hours to many days.^{7, 12} When life is spared beyond this time, various neurologic changes will exist.¹³ Some of these will be permanent, and others will clear up completely.¹⁴ Blindness, deafness, Parkinsonian syndrome, athetoid and choreiform movements, speech defects and emotional instability are some of the sequelae in these cases.¹

This leads to the conclusion that the outstanding pathological result of cardiorespiratory arrest is the damage to the brain produced by anoxia.

Pathology leading to cardiorespiratory arrest

Cardiorespiratory arrest can occur when respiration and circulation fail simultaneously. Frequently, however, either respiration or circulation fails first, and the failure of the other function follows. Which of these functions fails first is immaterial,¹⁵ for each is dependent upon the other. When respiration ceases, from whatever cause, the progressive oxygen deficiency that follows depresses the mechanism of circulation until in a few minutes circulation ceases. Conversely, any condition that results in failure of circulation⁵ will very soon produce failure of respiration from anoxia. Experiments on cats in which the pulmonary artery was ligated showed that in thirty seconds blood pressure was unobtainable and in forty seconds breathing ceased, when the occlusion was relieved in less than three minutes, the animals recovered, after three minutes resuscitation was necessary, after four minutes, even with successful resuscitation, there were permanent neurologic changes.¹⁶ By oxygenation of the blood extracorporeally, survival times were notably prolonged. It has been demonstrated that the human brain is not so capable as that of the dog of withstanding suspension of circulation and returning to normal.¹⁷

Respiratory arrest The frequent causes of respiratory arrest are as follows: paralysis of the respiratory musculature—for example, that which occurs in excessive curarization¹⁸ or in spinal anesthesia when the anesthetic level reaches the upper cervical segments^{19, 20}, paralysis of the respiratory center which may be produced by various drugs such as anesthetics,^{5, 21} hypnotics and analgesics or by reflex effect such as that occurring during anesthesia when

a gross stimulus and insufficient depth of general anesthesia are present²² (another important factor in the production of central respiratory paralysis is the anoxia that develops from respiratory obstruction⁵)

In contrast to the above types of respiratory arrest, there is a condition in which cessation of spontaneous respiration occurs without any danger to the patient. In this case, the anesthesiologist deliberately produces respiratory arrest by the "apneic technic" in which he takes over the function of pulmonary ventilation from the patient.²³ This procedure, which is readily reversible, is based on the physiologic phenomenon of eliminating carbon dioxide excessively and thus depriving the respiratory center of its physiologic stimulus. At the same time, oxygenation is not interrupted. This technic is a common practice in anesthesia.

Cardiac arrest. Circulatory failure may be of two fundamental types: cardiovascular collapse typified by shock (a discussion of this subject has been deemed beyond the scope of this review), and cardiac arrest in which the causative factors have acted upon the heart or upon autonomic centers that control heart action and have resulted in the disqualification of the heart as the motive force in circulation.

In such an event as cardiac arrest, there are two possibilities: the ventricles are fibrillating, or the heart is at a standstill. Ventricular fibrillation has been described by Guedel²⁴ as "a wormlike movement of the ventricular muscle with the heart in full diastole. It consists of an unsynchronized contraction and relaxation of the individual muscle fibres which provide no circulation of blood." Thompson et al.²⁵ described ventricular fibrillation as an "electrodynamic dissolution of the cardiac cycle."

Development of ventricular fibrillation in dogs after occlusion of the circumflex branch of the left coronary artery is characterized by the occurrence of isolated extrasystoles, this is followed by long runs of ventricular extrasystoles, and then by irregular ventricular complexes that become increasingly rapid and finally are converted to ventricular fibrillation.²⁶ In the operating room the common cardiac dysrhythmias observed are ventricular and auricular extrasystoles, tachycardia, foci of ectopic beats and shifting pacemaker, any one of which may be the precursor of ventricular fibrillation.²⁷ It has been noted that manipulations of the heart producing changes in its position or stimulation to the epicardium are prone to result in cardiac arrhythmias and that when ventricular extrasystoles or ventricular tachycardia occurs very often ventricular fibrillation follows.^{28, 29} Factors of etiologic significance in ventricular fibrillation¹⁰ include agents that sensitize the heart by their own action such as cyclopropane, chloroform and ethyl

chloride³⁰, hypoxia, which increases myocardial irritability and also causes an increase in epinephrine output³¹, emotional states such as fear by virtue of stimulating an outpouring of epinephrine³², and excessive vagal stimulation.³²

Danielopolu and Marcou³³ pointed out that in dog and cat experiments, ventricular fibrillation is often produced by asphyxia, chloroform and manipulation of abdominal viscera. Other demonstrations have proved that ischemia of the myocardium of the dog markedly reduces the fibrillation threshold of the heart to artificial stimuli.³⁴ Harken and Norman²⁷ classify the factors that can be responsible for cardiac arrhythmias as follows: reflex mechanisms,³⁴ which are related to the position of the patient during operation, intratracheal, intrabronchial and intrapulmonic stimulation, chest-wall manipulation and sudden alterations in blood volume, chemical changes in the blood stream, particularly, hypoxia and toxicity or sensitivity to drugs, and direct cardiac and intracardiac manipulation producing pericardial, epicardial or myocardial stimulation, and dislocation of the heart from its position of optimum function.²⁸

Stutzman and his co-workers³⁰ observed that ventricular fibrillation occurring under cyclopropane anesthesia is dependent upon a reflex. This reflex has its receptors in the abdominal viscera, particularly in the mesentery from which autonomic afferent pathways travel to a brain center above the pons, from there, efferent pathways lead by way of the sympathetic nervous system to the heart.

Little has appeared in the literature regarding the pathology of the condition termed cardiac standstill as compared to ventricular fibrillation. This state, which is characterized by the complete absence of activity of the myocardium,³² "the asystolic heart,"³⁵ may develop suddenly owing to an overwhelming vagal reflex³ or may develop gradually in relation to hypoxia when progressive weakening of contractions occurs. When the state of standstill is reached, the heart is in some degree of dilatation, and the irritability of the myocardium is relatively low. If the irritability of such a heart is increased, at some point the myocardium may start to fibrillate.³⁶ The presence of anoxia may support the change from cardiac standstill to ventricular fibrillation. For practical purposes, the heart that is not asystolic but has feeble, ineffective contractions can be considered in the same category as the heart in standstill.

Pharmacologic Action of Drugs on the Brain and Heart in Cardiorespiratory Arrest

The susceptibility or resistance of the brain to anoxia depends largely on the state of its cellular activity. The highly active brain having a high oxygen demand will suffer more from oxygen lack, whereas the brain whose function is depressed can resist anoxia to some extent.³⁷ Drugs that stimulate

the central nervous system will increase its oxygen demand, thus, in cardiorespiratory arrest such drugs will aggravate the danger of damage from anoxia³⁸ For this reason, analeptic and sympathomimetic drugs, such as caffeine, coramine, metrazol, strychnine, ephedrine, Benzedrine, Neo-Synephrine and paredrine, which formerly were called upon in cardiorespiratory emergencies, are condemned⁵ Conversely, drugs such as anesthetics and analgesics³⁸ that depress the central nervous system and thereby decrease its oxygen demand may be responsible for prolonging the survival time of the brain cells during periods of anoxia^{14 39}

Epinephrine stimulates the heart by a direct effect on the myocardium and on the conduction tissue^{40 41}, it produces more forceful contractions of the myocardium³⁶ Objections raised against the use of epinephrine in cardiorespiratory arrest are based upon its ability to increase myocardial irritability,^{14 30 42-44} to elevate markedly the oxygen consumption of the heart muscle⁴⁵ and to increase the speed of auriculoventricular conduction time Because of these properties, when epinephrine is administered in the presence of a failing heart in which a state of cardiac standstill or a prefibrillation arrhythmia exists, it may produce ventricular fibrillation When the drug is used, Hyman³⁵ and Mautz⁴⁵ recommend that it be injected into the heart muscle, where it is most effective, Harken and Norman²⁷ recommend that it be injected into the right ventricle, whereas Dripps et al¹⁴ choose injection into the auricle, where it is least likely to cause ventricular fibrillation

Procaine hydrochloride diminishes the irritability of the conduction system of the heart and of the myocardium, thereby causing reversion of prefibrillation dysrhythmias to normal rhythm⁴⁶ Hence it has a definite *protecting effect* on the heart against ventricular fibrillation^{42 43 45 47 48} On the other hand, although admitting that procaine raises the fibrillation threshold of the ventricles, Wiggers and Wegria⁴⁹ and Fauteux⁵⁰ believe that procaine does not prevent ventricular fibrillation This contention is supported by a case reported by Harken and Norman²⁷ in which ventricular fibrillation occurred after the patient had been "procainized"

The role of procaine in *defibrillation*—that is, reversal of ventricular fibrillation—of the heart is questionable Stutzman et al⁵¹ failed to control ventricular fibrillation induced by cyclopropane-epinephrine with the intravenous injection of procaine Harken and Zoll⁵² corroborated these experiences On the other hand, a number of reports demonstrate the successful use of procaine in defibrillation of the heart^{13 26 44 45 48 53} Procaine is recommended for intravenous administration in 1 per cent solution⁴⁵, doses are 40 to 100 mg in single injections up to a maximum of 200 mg⁵⁴

Atropine and scopolamine by virtue of their blocking of vagal effects on the sinoauricular pace-

maker protect the heart to some extent against reflexes that may precipitate cardiorespiratory arrest^{25 55}

In addition to their main effect on the myocardium digitalis and strophanthin act upon the auriculoventricular conduction system to increase the refractory period and slow the rate of conduction⁵⁶ The latter action protects the heart to some extent in states of increased irritability Toxic effects from these drugs on the heart may result in arrhythmias of which ventricular tachycardia is the most serious, this may be the precursor of ventricular fibrillation⁵⁶

Quinidine acts upon the heart to decrease myocardial excitability and to slow conduction of impulses in the heart muscle thereby reducing the danger of ventricular fibrillation It has attained some favor as a preventive measure when it is given preoperatively in the presence of all cardiac arrhythmias with the exception of auricular fibrillation^{26 27 45 57}

Calcium chloride and barium chloride are cardiac stimulants that increase the force of myocardial contractions^{50 58}

Potassium relaxes the myocardium, it may produce cardiac inhibition and stop ventricular fibrillation^{56 58 59}

Effect of Electric Stimulation upon the Heart

When an electric current of sufficient strength is accidentally passed through the body it may cause ventricular fibrillation or cardiac standstill from inhibition of the conduction mechanism or paralysis of the myocardium^{6 59} Experimental work has demonstrated that it is possible to apply an electric current to the heart for therapeutic purposes Wiggers⁶⁰ introduced a method of treating ventricular fibrillation (the technic of "serial defibrillation") in which he applied a momentary shock 1.0 ampere in strength of a 60-cycle alternating current, through two electrodes, which were placed on opposite sides of the heart Three to seven shocks were required to stop fibrillation He reasoned that each shock resulted in the merging of small fibrillating areas into progressively larger ones until with the final shock all fibrillation was arrested At this moment cardiac standstill was produced and the problem of reinstituting rhythmic cardiac activity remained

Experiences of Hooker et al,⁶¹ Beck and his co-workers⁶² and Lampson and his associates⁴⁴ have confirmed the usefulness of this procedure in defibrillation of the heart The equipment required is relatively simple

Diagnosis of Cardiorespiratory Arrest

The diagnosis of respiratory arrest does not present any problem, for cessation of respiration can readily be observed But the recognition of cardiac arrest may be quite difficult⁴⁴ If the opera-

a gross stimulus and insufficient depth of general anesthesia are present²² (another important factor in the production of central respiratory paralysis is the anoxia that develops from respiratory obstruction⁵)

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ecuted and the patient does not seem to have adequate excursions of the thorax the air passages are obstructed. It is then necessary to insert oral nasal or tracheal airways or to remove any foreign material that may be causing the obstruction.¹⁰ The interruption of the administration of oxygen while such manipulations take place must be for the briefest possible time. When an anesthesia machine is not available in the operating room, the same intermittent administration of oxygen may be accomplished by a simple arrangement consisting of a face mask, rubber rebreathing bag and cylinder of oxygen.²⁵ No operating room should function without an anesthesia machine or, at the very least, the latter equipment.

Mautz⁷¹ has described an attachment to the anesthesia machine that utilizes compressed air as the source of the force that ventilates the lungs. Kreiselman's⁷² resuscitator produces intermittent flow of oxygen under adjustable positive pressure. Other less simple apparatus that effect rhythmic inflation of the lungs followed by rhythmic suction—so-called "suck and blow" resuscitators—are recommended by Thompson et al.^{25, 73, 74} and Schwerma and his co-workers.⁷⁵

It has been pointed out that in addition to providing efficient pulmonary ventilation the application of alternating positive and negative pressure has beneficial effects on the circulation and initiates stimulatory impulses for respiration.^{73, 74, 76, 77} Disapproval of these resuscitators is based upon the possibility of damage to the lungs and the fact that unskilled application greatly reduces their usefulness and exposes the circulation to harmful effects.^{75, 79} Mousel, Stubbs and Kreiselman⁵ state that such apparatus should not be relied upon in these emergencies.

A recently introduced method of artificial respiration employs electric stimulation of the phrenic nerve thereby producing rhythmic contractions of the diaphragm, which will provide adequate pulmonary ventilation.⁸⁰⁻⁸² Practical considerations at present limit this promising method.

In cases where the anesthesia machine or the simple arrangement referred to above is not available in the operating room (the existence of such a deplorable situation must be condemned) methods of manual artificial respiration or mouth-to-mouth insufflation must be resorted to. Of the manual methods, the rib-retraction technic of Viswanathan⁸³ is regarded as superior to the method of Schafer⁸⁴ or Silvester.⁸⁵ These manual methods of artificial respiration are difficult and unsatisfactory.⁵

Artificial circulation For re-establishing circulation several approaches are described.

Employment of an extracorporeal pump as the source of motive power in the circulation has been mentioned but is not as yet available.^{16, 27, 48}

Another approach to the problem includes mechanical stimuli³⁵ such as needle puncture^{25, 87} of the heart, percussion²⁵ and compression¹⁵ of the chest wall, and incision or pinching³³ of the pericardium. Intracardiac injections of epinephrine, procaine or Neo-Synephrine,⁸⁸ or a combination of procaine and epinephrine,¹⁰ and intravenous injections of drugs such as ether, caffeine sodium thiosulfate, Ronzini's solution, camphor, digitalis, strophanthin, Metrazol, coramine strychnine, 20 per cent dextrose and hypertonic saline solution have all had their proponents.³⁵ Beneficial results following some of these measures are reported, however, uncertainty regarding indications for and outcome of this approach is obvious.

The third approach employs the heart as the pump of the circulation, but utilizes the force from the operator's hand rather than that of the myocardium. This method of manual compression (cardiac massage) requires adequate exposure of the heart. The direct approach through the chest wall by a transverse incision in the fourth left intercostal space, with division of the fourth and fifth costal cartilages, is believed to be superior to an abdominal incision with an attempt to reach the heart through either an intact or an incised diaphragm.^{2, 14, 64, 89} The heart is grasped and compressed firmly at the rate of twenty to forty times a minute, depending upon the adequacy with which the ventricles fill between compressions.^{14, 27} With effective cardiac massage, the radial pulse often can be felt and the blood pressure may be as much as 60 or 70.¹⁴ To increase blood flow through the coronary arteries and the brain, the clamping of the aorta distal to the left carotid artery may be helpful.²⁷ Cardiac massage is the most efficient method of providing for artificial circulation and is first choice in the technic of cardiac resuscitation.^{2, 14, 27, 64, 89}

Why this is not fully appreciated is probably due to the general lack of familiarity with the technic. It is hoped that this relatively simple, life-saving surgical procedure will be included among the fundamental essentials in undergraduate and postgraduate surgical training.^{15, 90}

A prearranged plan for meeting the emergency of cardiorespiratory arrest with a specific assignment for each member of the operating-room team is recommended.^{64, 90}

When the first goal of resuscitation—that of oxygenation of the tissues by the administration of artificial respiration (for which the anesthesiologist with his machine is best suited)—with the simultaneous production of artificial circulation by cardiac massage (which is best performed by the surgeon²⁹) has been attained the second aim of resuscitation may be pursued without confusion and haste.

tive wound does not permit the inspection or palpation of the heart or a major artery, there is little reliable guide for positive diagnosis. The situation that may occur at this time is aptly described by Dripps and his colleagues¹⁴: "The majority of patients are doomed because minutes which cannot be spared are wasted in searching for a stethoscope, in frantic palpation of a succession of arteries, in hasty consultation with colleagues summoned to judge a situation with which they are unfamiliar."

Various diagnostic procedures such as visualization of pulsations of the retinal vessels through an ophthalmoscope,¹⁴ inhalation of amyl nitrite to stimulate forceful contractions in a feebly beating heart,⁶⁵ observation of the speed of capillary refill¹⁴ and examination of an electrocardiographic tracing⁶⁵ are either unreliable or impractical.¹⁴ Therefore, in the words of Dripps and his co-workers:

Opening the thorax is the only conclusive diagnostic procedure. If the heart has stopped or the ventricles are fibrillating, minutes can be saved by adopting the attitude of rapidly opening the chest for diagnosis, whereas if the heart is beating feebly, little harm may have been done.

In cardiorespiratory arrest the clinical judgment of the anesthesiologist, who has closely observed the patient during the preceding period and who is aware of the internal and external factors that may have affected the patient's physiology, plays an important role in the evaluation of this emergency.

Prophylaxis

Undoubtedly the most important factors in the prophylaxis of cardiorespiratory arrest lie in the anesthetic management of the patient. Mousel and his associates⁵ state that the intelligent and judicious handling of the patient in the preoperative period and during anesthesia will prevent most of the harmful sequelae.⁴⁰

In the preoperative period, protective measures calculated to diminish the incidence of cardiorespiratory accidents are as follows: regulation of fluid and electrolyte balance, restriction of water and sodium intake in elderly patients and those having poor cardiorenal reserves, the proper use of digitalis and quimidine in selected cases, and the careful choice of premedicating agents that allay excitement and irritability, reduce oxygen need and inhibit parasympathetic functions.²⁷

The most important preventive measure during anesthesia is the maintenance of adequate oxygenation at all times. Ruth,⁶⁶ in his studies of anesthetic accidents, found that the most common error during the period preceding the accident was that the anesthetist tolerated anoxia in his patient.

Of similar importance is the proper selection of anesthetic agents and their skillful administration. A specific preventive measure is intravenous in-

jection of procaine or procaine applied topically to the pericardium during thoracic operations.²⁷ To protect the patient from ventricular fibrillation that may occur under cyclopropane anesthesia, the addition of ether to the inhaled gases is recommended. On the basis of the findings of Stutzman et al.³⁰ it seems likely that a spinal anesthetic administered prior to cyclopropane anesthesia has a similar protecting effect.

Finally, and by no means any less in importance, is the close co-operation between the surgeon and anesthetist that is necessary in minimizing manipulations, especially during light anesthesia, which may initiate dangerous reflexes.²⁸

Treatment of Cardiorespiratory Arrest

Two aims are apparent in the treatment of cardiorespiratory arrest.

The first and immediate goal is to deliver oxygen to the tissues. Whether or not life is saved, or, if life is spared, whether or not permanent brain damage is suffered, is dependent upon the early and successful accomplishment of the foregoing principle.^{1, 10, 61} The first aim is attained by simultaneously providing ventilation of the lungs by artificial respiration and artificial circulation by cardiac massage. By these procedures, oxygen is taken into the alveoli of the lungs, from which it is transported by the blood and delivered to all the body tissues. When this is accomplished, the greatest immediate danger — namely, that the cardiorespiratory arrest will become irreversible — is passed.

Artificial respiration. The fundamental principles that must be observed in artificial respiration are as follows:⁶³ intermittent rhythmic exchange of atmosphere in the patient's lungs must be started at the rate of sixteen to twenty times a minute, any obstruction of the throat and air passages must be relieved as quickly as possible, and adequate time must be allowed for the lungs to empty after each inflation.

Since the production of the highest possible concentration of oxygen in the alveoli of the lungs is desired, 100 per cent oxygen should be used.^{10, 63} The opinion is commonly held that carbon dioxide should not be added to oxygen for resuscitative purposes because the patient whose respiration has ceased is unable to eliminate carbon dioxide retained in his blood and tissues.^{5, 63} If artificial sources of oxygen are not available, atmospheric air or even the exhaled air of the operator may be used.

In the operating room, where cardiorespiratory arrest is most likely to occur, artificial respiration is best accomplished by rhythmic compression, with the force equivalent to about 20 mm of mercury, on the breathing bag of the anesthesia machine.^{69, 70} This must be promptly instituted after spontaneous respiration has ceased. If this intermittent administration of oxygen is properly ex-

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The second aim is to re-establish the vital functions — spontaneous heart action and respiration — and to attain complete recovery of the patient

The recommended treatment when the heart has been found in ventricular fibrillation is serial defibrillation and the intravenous administration of procaine^{15 42 43 62}. Intracardiac injection of 10 cc of 1 per cent potassium chloride may be helpful in defibrillating the heart^{55 59}. After defibrillation, the situation is identical with that of cardiac standstill, and effective cardiac massage is the most important measure until spontaneous rhythmic contractions are resumed^{14 27 29}. When contractions start, they may be quite feeble. At this time, the administration of 0.5 cc of a 1:1000 solution of epinephrine into the right ventricle^{14 27} or auricle will help strengthen the heart beat. This is perhaps the only place for administration of epinephrine in cardiac resuscitation^{27 29 44}. The injection of 1 or 2 cc of 0.5 per cent solution of barium chloride^{36 50 51} or 10 cc of 1 per cent solution of calcium chloride^{20 45} into the heart serves the same purpose.

Resumption of spontaneous respiration does not require any specific measures. If proper oxygenation of the brain has been maintained, respiration will be re-established when the respiratory center recovers from the depression incident to cardiorespiratory arrest.

In order to further the attainment of complete recovery, adjunctive therapy is desirable: continuation of inhalation therapy through a free airway and attention to maintaining an adequate urinary output by supplying sufficient fluids and electrolytes are indicated. Prophylactic measures for the prevention of pulmonary infection, hypostatic congestion and distention of the bladder are necessary.¹⁴

Prognosis

Dripps and his associates¹⁴ state that, in general, if prompt diagnosis is followed by prompt therapy, the heart beat can be restarted. This thesis is supported by the studies of Kountz,⁹¹ who examined the hearts of persons a short time after death and demonstrated that the heart is an amazingly resistant organ possessing rhythmicity and contractility that are difficult to destroy.

Factors such as the time element in instituting effective therapy, the age of the patient and the cardiac status prior to the catastrophe will ultimately determine whether the heart can be restored to normal function.¹⁴ The anoxia that develops because of delay in diagnosis and in establishing effective artificial respiration and cardiac massage may so damage the myocardium that it resists all efforts at resuscitation. The myocardium damaged by pre-existing toxemia, arteriosclerosis, hypertension, coronary insufficiency or narcosis is much less likely to recover.¹⁴ Wiggers⁴⁹ found that failure to recover from ventricular fibrillation de-

pended not so much on the inability to defibrillate the heart as on the subsequent inability of the myocardium to resume vigorous beating.^{50 62}

If the heart returns to regular rhythm and blood pressure is maintained, what will be the status of the central nervous system? The prognosis is determined by the duration of cerebral anoxia.¹⁴ Clinical experiences as well as the work of Weinberger, Gibbon and Gibbon⁹² indicate that if the cardiorespiratory arrest has not exceeded two to four minutes, complete recovery may be expected. This is well illustrated by more than 70 cases reported with complete recovery.^{2 10 12 14 22 44 53 67 64 89 90}

Spontaneous respiratory activity may be expected to reappear within five to thirty minutes once cardiac activity has been resumed. If cardiorespiratory arrest has been slightly more prolonged, convalescence may be stormy but may show progressive improvement with each passing hour.¹⁴ This period is characterized by acute febrile responses, muscular rigidity, twitching, convulsions, hyperflexia and varying degrees of coma.^{1 14} The time of onset and the duration of these phenomena are prognostically significant. The persistence of coma beyond the first twelve hours is an unfavorable finding. In this case, consciousness is not likely to return, and the heart may again cease to beat within a few minutes to several weeks. If consciousness is regained, partial recovery — that in which residual neurologic symptoms persist — or complete recovery may follow.¹¹

* * *

Commenting on the problem of cardiac resuscitation, Dripps and his colleagues¹⁴ emphasize the necessity for greater awareness on the part of the anesthesiologist and surgeon of the implications of this accident. They also raise the question of approaching the problem from other points of view. What are the possibilities of protecting the brain from anoxia by preoperative measures, and what are the roles of intra-arterial and intracardiac infusions? Of what value will the oxyhemograph be in diagnosis of anoxia and prevention of cardiorespiratory arrest?^{742 92 96}

These seem to be problems for the future. The greatest problem of the present is pointed out by Mousel, Kreiselman and Stubbs who emphasize the fact that the conduction of an anesthesia expressly designed to prevent complications is of the utmost importance. They claim that the incidence of fatal accidents is more than twenty times greater in institutions where the type of anesthetic organization is poor or even average as compared to that in institutions where the best in anesthesia is available. This is understandable since the special knowledge and skill of the anesthesiologist may nowhere be more valuable than in the prevention diagnosis and treatment of cardiorespiratory arrest.

(To be concluded)

dice, spider-type telangiectasia on the skin, a Grade II pulmonic systolic murmur, bilateral basal inspiratory rales and a tender firm liver edge, palpable three fingerbreadths below the costal margin.

The blood pressure was 120 systolic, 80 diastolic. The temperature was 100°F by rectum, the pulse 90, and the respirations 18.

Examination of the blood showed a white-cell count of 4000, with 51 per cent neutrophils, 40 per cent lymphocytes, 8 per cent monocytes, and 1 per cent eosinophils. The urine specific gravity was 1.015, with a +++ test for bile, and the sediment was normal. The stools were guaiac negative and bile positive. The serum alkaline phosphatase was 9.6 units per 100 cc, the prothrombin time 28 seconds (control, 15 seconds), and the cholesterol 161 mg, and the cholesterol esters 44 mg per 100 cc, the serum albumin was 2.6 gm per 100 cc, and a globulin of 3.7 gm. The nonprotein nitrogen was 24 mg per 100 cc, and the van den Bergh reaction 11.2 mg per 100 cc direct, 17.4 mg indirect. The cephalin flocculation was +++ in twenty-four hours, the thymol turbidity ++, and the urinary urobilinogen 6.5 Ehrlich units.

A gastrointestinal series demonstrated esophageal varices. The spleen was enlarged. There was no evidence of opaque calculi in the region of the gall bladder.

In the hospital the patient's appetite was poor, and dependent edema and ascites appeared. Therapy included mercurial diuretics, intravenous injection of albumin, a high-calorie, high-carbohydrate and high-protein diet and vitamin K. Oliguria appeared and was persistent. Drowsiness and stupor followed. In the last two weeks in the hospital the temperature was irregularly elevated.

The temperature reached 104 to 105°F, where it persisted for two days, when she died, one month after admission.

DIFFERENTIAL DIAGNOSIS

DR ALFRED E. KRANES: There are a number of interesting features about this problem. When I first read it, I was very much impressed by the apparent and striking discrepancy between the history and the laboratory findings. To me, the history was suggestive of disease of the extrahepatic biliary ducts, and if the pain could in any way be fitted into the terminal illness, it seemed reasonable to ascribe it to intermittent obstruction of the biliary ducts. And yet, when we come to the terminal illness, one is struck by the fact that all the laboratory findings given here point almost unequivocally to intrahepatic disease. Certainly, the presence of bile in the stools, the positive cephalin-flocculation test, the cholesterol finding and the marked urobilinogenuria point, without much question, to intrinsic disease of the liver. I have always believed that when the laboratory

findings and the history are at variance, it is always better to disregard the laboratory findings and rely on the history if it is a good one. However, I do not see how it is possible to disregard the impressive array of evidence for intrahepatic disease in this case. Furthermore, we have x-ray evidence of esophageal varices, which always mean to me diffuse fibrosis of the liver. May we see these films now?

DR STANLEY M. WYMAN: The varices are well demonstrated in the lower esophagus, there being apparently several quite large, tortuous vessels. The spleen is at the upper limits of normal, if not definitely enlarged. There seems to be a compression of the superior lateral aspect of the duodenal cap, possibly from the liver or from the gall bladder. There may even be some tortuosity of the folds of the stomach over and above what one expects, to raise the question of varices in the stomach.

DR KRANES: I wonder if anyone has any idea how long it would take for varices to appear? Let us put it this way. In how short a time may varices appear?

DR TRACY B. MALLORY: In a well documented case of post-necrotic cirrhosis following hepatitis that Wallgren¹ reported, the patient, a young boy, died of ruptured esophageal varices eight months after acute hepatitis.

DR KRANES: You certainly would not expect it to occur before several years in the usual case, would you?

DR MALLORY: I think it could occur in a period as short as two or three years.

DR MYLES P. BAKER: Dr Schatzki told me that four years was about the shortest time.

DR KRANES: It is a difficult determination to make, but it is of interest in this case.

To go back to the history for a moment, what interested me very much was how the patient with this history was able to escape more in the way of surgery or diagnostic studies over a period of twenty years. Because this history of twenty years is being compressed into a very short space, it may be that some relevant information was left out.

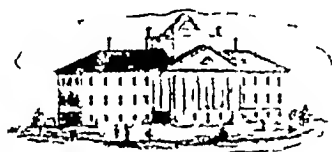
DR MALLORY: I have seen doctors and nurses do just that, Dr Kranes.

DR KRANES: Yes, and this patient was a nurse. She may have been an extremely stoical person and may not have consulted anyone.

It does surprise me that during twenty years no Graham test was done, and no other studies carried out. I am also intrigued by the innocent sounding statement, "When an appendectomy was performed several years before admission an infantile uterus was found." I must confess that I am more interested in what the gall bladder looked like at that operation, than in how the uterus appeared. Again, we have no information at all about that. Do we know whether the incision was made in the lower abdomen? I wonder why the operation was

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 35361

PRESENTATION OF CASE

A thirty-nine-year-old practical nurse was admitted to the hospital complaining of jaundice.

Twenty years before admission she had an attack of "acute indigestion." Her physician diagnosed a gall-bladder attack, but it subsided overnight and no operation was performed. In the subsequent two decades she had repeated attacks of similar pain. It was characterized by epigastric discomfort, "as if you had a stone and tried to push it through something and it won't go," and sometimes by an ache, radiating occasionally to both sides of the upper abdomen, to the right back and to the shoulder. The duration of the pain varied from thirty minutes to five hours. It was often more severe at night, and sometimes awakened the patient from sleep. The onset of pain

was sudden. Nausea was sometimes present during attacks. There was no vomiting. The attacks occurred about once monthly, but had increased in frequency in the past several years. She went on a fat-free diet at one time without relief. Ten months before admission, she had slight malaise, "dry eyes" and a temperature of 103°F. On the following day she felt well. This phenomenon occurred every two to four weeks. There were no chills or associated abdominal pain. Eight months before admission she noted easy fatigability and weakness. One month before admission mild itching appeared at night, but it subsided in the past two weeks. Three weeks before admission jaundice, dark urine and fever appeared, and persisted. The temperature sometimes reached 103°F. There was no change in the color of the stools. She had received no blood transfusions and had had no recent exposure to others with jaundice. There was no alcoholic consumption, her appetite remained good, and food intake was unrelated to pain.

One week before admission she entered a community hospital, where the following were noted: jaundice, extreme right-upper-quadrant tenderness and a palpable and slightly tender liver edge. The serum albumin was 4.0 gm per 100 cc, with a globulin of 2.8 gm, the prothrombin time 47 seconds (normal, 16 seconds), the blood Hinton reaction negative, the icteric index 57 per cent, the bleeding time 1½ minutes and the clotting time 5½ minutes.

The patient had never menstruated. When an appendectomy was performed several years before admission an infantile uterus was found. There had been occasional swelling around the ankles on prolonged standing.

When she was transferred to this hospital for further study physical examination showed jaun-

DR KRANES That is an interesting point and one that I should have brought out in the discussion. During the course of the ordinary portal cirrhosis, one occasionally sees patients with severe attacks of upper abdominal pain — and sometimes right-upper-quadrant pain — mimicking biliary colic in many respects, and at autopsy there appears to be no morphologic explanation.

CLINICAL DIAGNOSES

Cholemia
Liver disease of unknown nature

DR KRANES'S DIAGNOSIS

Cirrhosis of liver, biliary type

ANATOMICAL DIAGNOSES

Portal cirrhosis of liver, postnecrotic type
Splenomegaly

PATHOLOGICAL DISCUSSION

DR MALLORY The one diagnostic measure that today is usually applied to a cirrhotic patient is that of an aspiration biopsy from the liver. In this case, it was never thought safe to do it because the prothrombin time could not be brought down to normal.

The autopsy was, unfortunately, limited to examination of the peritoneal cavity so that I cannot give complete findings. However, the liver, which had been reported as three or four fingerbreadths below the costal margin, weighed only 750 gm — barely half normal. It was shrunken diffusely fibrotic coarsely nodular and rather characteristic of the postnecrotic type of portal cirrhosis. The gall bladder and extrahepatic ducts were normal, with no stones and no evidence of cholangitis. Either post mortem or in the agonal period a gas-bacillus infection had developed, and there were a great many gas bubbles throughout the liver, making the histology rather poor. But still, I think, we can safely eliminate cholangitis and feel sure that it was a postnecrotic type of cirrhosis. I believe the multiple attacks of pain were of the type that one sees in portal cirrhosis that can mimic gall-bladder colic in a fashion that often leads to exploration and nothing is found to explain it.

DR BAKER Do you think this started originally with acute viral hepatitis without any necrosis and went to the point of cirrhosis?

DR MALLORY It could have been. It would be indistinguishable from the type that we see in patients following arsenical or cinchophen therapy and so forth.

DR KRANES One would have to assume that these attacks of upper abdominal pain due to portal cirrhosis had been present for twenty years.

DR MALLORY I think that is possible. It was an old, inactive process. The spleen was estimated as weighing 900 gm — markedly enlarged.

DR KRANES How about the attacks of fever? They are not very well explained.

DR MALLORY There is no adequate explanation. But, as I say, we did not have a complete autopsy. We might have found something in another part of the body to account for it. I do not believe that this gas-bacillus infection could have existed for more than a few hours before death.

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CASE 35362

PRESENTATION OF CASE

A fifty-one-year-old painter was admitted to the hospital because of vomiting and gnawing epigastric pain.

The present illness dated back some twenty-five years before, when he first noticed the onset of gnawing epigastric pain, occasional vomiting and "indigestion" relieved by sodium bicarbonate. X-ray examination at that time revealed a peptic ulcer. On therapy, consisting largely of diet, the patient became asymptomatic rather rapidly. One year later he discontinued his diet and since that time had intermittent recurrence of mild to moderate distress. Two years before admission he noticed the onset of occasional vomiting. Following a gastrointestinal series taken a few months later he was told that there was some obstruction at the site of the old ulcer. During the two months before entry to the hospital he had increasing difficulty retaining food and vomited frequently. He lost about 16 pounds of weight during this period. At no time had there been hematemesis or melena. A review of the systems revealed that the patient had had frequency and mild burning on urination during the recurrences of the gastrointestinal symptoms. He had nocturia every two hours during the two-month episode that brought him to the hospital. He had noted no hematuria, chills, fever or costovertebral-angle tenderness.

Physical examination revealed a well nourished, well developed man in no apparent distress. The chest was clear, the heart was normal. The abdomen showed only hyperperistalsis.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood disclosed a nonprotein nitrogen of 39 mg and a total protein of 6.6 gm per 100 cc. The blood chloride was 98 milliequivalents per liter. The phenolsulfonphthalein test showed 33 per cent excretion of the dye in two hours. The blood hemoglobin was 12.9 gm. The white-cell

done — I suppose for the attacks of pain that she had

DR MALLORY It was a midline lower abdominal incision — 18 cm long, however

DR KRANES I was about to say that the surgeons may have operated expecting to find disease of the gall bladder, and, not being able to find it, they simply removed the appendix. An incision in the lower abdomen would be somewhat against that explanation. An 18-cm incision is somewhat in favor of it. It would be helpful to know whether or not she had any abnormality of the gall bladder. Apparently, we will not find out until Dr Mallory tells us.

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usually due to stones, although not necessarily. It can sometimes follow an inflammatory stricture of the bile duct, and occasionally there are cases in which no obstructive lesions in the bile duct are found. I should think, however, with this history of repeated attacks of pain, that it is highly likely stones will be found, if not in the common duct, possibly in the hepatic ducts. The patient also had cholangitis as evidenced by the periodic attacks of fever, finally becoming much more marked toward the end. Occasionally these patients will have, and this patient may have had, a terminal illness, with supuration around the small bile radicles in the liver, as evidenced by high fever and extreme tenderness of the liver. Many of these patients in more acute phases have multiple abscesses in the liver.

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Can we consider any other type of lesion in this patient? I hardly think so, although if this patient had a diseased gall bladder for twenty years, one must mention the possibility of carcinoma of the gall bladder. I can see nothing in the record that permits one to make such a diagnosis. So, I shall end up by saying that this patient had cirrhosis of the liver and by guessing that the cirrhosis was probably of the type I have mentioned.

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DR KRANES That is an interesting point and one that I should have brought out in the discussion. During the course of the ordinary portal cirrhosis, one occasionally sees patients with severe attacks of upper abdominal pain — and sometimes right-upper-quadrant pain — mimicking biliary colic in many respects, and at autopsy there appears to be no morphologic explanation.

CLINICAL DIAGNOSES

Cholemia
Liver disease of unknown nature

DR KRANES'S DIAGNOSIS

Cirrhosis of liver, biliary type

ANATOMICAL DIAGNOSES

Portal cirrhosis of liver, postnecrotic type
Splenomegaly

PATHOLOGICAL DISCUSSION

DR MALLORY The one diagnostic measure that today is usually applied to a cirrhotic patient is that of an aspiration biopsy from the liver. In this case, it was never thought safe to do it because the prothrombin time could not be brought down to normal.

The autopsy was, unfortunately, limited to examination of the peritoneal cavity so that I cannot give complete findings. However, the liver, which had been reported as three or four fingerbreadths below the costal margin, weighed only 750 gm — barely half normal. It was shrunken, diffusely fibrotic, coarsely nodular and rather characteristic of the postnecrotic type of portal cirrhosis. The gall bladder and extrahepatic ducts were normal, with no stones and no evidence of cholangitis. Either post mortem or in the agonal period a gas-bacillus infection had developed, and there were a great many gas bubbles throughout the liver, making the histology rather poor. But still, I think, we can safely eliminate cholangitis and feel sure that it was a postnecrotic type of cirrhosis. I believe the multiple attacks of pain were of the type that one sees in portal cirrhosis that can mimic gall-bladder colic in a fashion that often leads to exploration, and nothing is found to explain it.

DR BAKER Do you think this started originally with acute viral hepatitis without any necrosis and went to the point of cirrhosis?

DR MALLORY It could have been. It would be indistinguishable from the type that we see in patients following arsenical or cinchophen therapy and so forth.

DR KRANES One would have to assume that these attacks of upper abdominal pain due to portal cirrhosis had been present for twenty years.

DR MALLORY I think that is possible. It was an old, inactive process. The spleen was estimated as weighing 900 gm — markedly enlarged.

DR KRANES How about the attacks of fever? They are not very well explained.

DR MALLORY There is no adequate explanation. But, as I say, we did not have a complete autopsy. We might have found something in another part of the body to account for it. I do not believe that this gas-bacillus infection could have existed for more than a few hours before death.

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CASE 35362

PRESENTATION OF CASE

A fifty-one-year-old painter was admitted to the hospital because of vomiting and gnawing epigastric pain.

The present illness dated back some twenty-five years before, when he first noticed the onset of gnawing epigastric pain, occasional vomiting and "indigestion" relieved by sodium bicarbonate. X-ray examination at that time revealed a peptic ulcer. On therapy, consisting largely of diet, the patient became asymptomatic rather rapidly. One year later he discontinued his diet and since that time had intermittent recurrence of mild to moderate distress. Two years before admission he noticed the onset of occasional vomiting. Following a gastrointestinal series taken a few months later, he was told that there was some obstruction at the site of the old ulcer. During the two months before entry to the hospital he had increasing difficulty retaining food and vomited frequently. He lost about 16 pounds of weight during this period. At no time had there been hematemesis or melena. A review of the systems revealed that the patient had had frequency and mild burning on urination during the recurrences of the gastrointestinal symptoms. He had nocturia every two hours during the two-month episode that brought him to the hospital. He had noted no hematuria, chills, fever or costovertebral-angle tenderness.

Physical examination revealed a well nourished, well developed man in no apparent distress. The chest was clear, the heart was normal. The abdomen showed only hyperperistalsis.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood disclosed a nonprotein nitrogen of 39 mg and a total protein of 6.6 gm per 100 cc. The blood chloride was 98 milliequiv per liter. The phenolsulfonphthalein test showed 33 per cent excretion of the dye in two hours. The blood hemoglobin was 12.9 gm. The white-cell

done — I suppose for the attacks of pain that she had

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remained rigid, especially in the right upper quadrant. The blood sodium had risen to 128 milliequivalents per liter.

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR FRANCIS D MOORE* I should like to know what the rectal examination showed with reference to the prostate and also what the urinary sediment showed.

DR TRACY B MALLORY The prostate was not enlarged or tender. Examination of the urinary sediment on admission was negative. That is the only comment we have — just negative.

DR MOORE This case is important from the point of view of time relations. I should like to review them before going into the details of the history. The patient apparently entered the hospital with a past history of both urinary and gastrointestinal symptoms. The urine culture was negative despite the gross urinary sediment found on cystoscopy, so we must assume that that was a laboratory error and that the patient's urine was not normal. When the cystoscope was first put in there was fibrin which is seen in the urine in cystitis and is accompanied by a high white-cell count in the sediment. Cystoscopy was done on the sixth day, and on the twelfth day a subtotal gastrectomy was carried out. Following that he had ten days of uneventful convalescence except for continuation of the urinary-tract infection. That is important because a patient who has had ten days of smooth convalescence after subtotal gastrectomy should rightfully be considered to be beyond the point where one could expect a blow-out either of the duodenal stump or of the other suture lines. Yet this time is too short for the development of a jejunal ulcer, so the interval is of some help to us. On the eleventh postoperative day things began to pile up. The x-ray examination showed delay at the gastric cardia, spasm and tenderness of the abdomen on the twelfth day, severe abdominal pain on the thirteenth day, and a distended abdomen on the fourteenth day.

As I see it there are two problems in this case. One is the nature of the renal lesion, the second is the nature of the intra-abdominal complications of the gastrectomy. He was fifty-one and a painter. When Dr Aub looked at the protocol he immediately assumed that this was the case he was to

discuss. The question of lead poisoning must be considered as a possibility in the background.

His illness began at twenty-six, which is the characteristic age for the onset of duodenal ulcer symptoms. X-ray studies revealed a duodenal ulcer at that time. I assume that the treatment of duodenal ulcer twenty-six years ago — as at present — consisted largely of diet. The patient became asymptomatic rapidly, again characteristic of duodenal ulcer in the young adult male. One year later he discontinued his diet, and since that time he had had intermittent recurrence of mild to moderate distress. It would be interesting and important to know what he did when his distress came back. Did he treat himself with alkali? Here is a patient with severe kidney disease. We wonder if he took calcium in the form of milk or powders or did he just avoid rich foods?

Twenty-four years later, he began to have obstructive symptoms. He was admitted to the hospital with genuine obstruction — I say "genuine" since he lost 10 pounds in weight. This history is quite consistent in itself with the history of duodenal ulcer, and I see no reason to doubt that diagnosis or to take any further time discussing it. The report was "healing duodenal ulcer." This is interesting because it suggests a little difficulty for the surgeon in doing a gastrectomy, which is significant when we later pause to consider possible complications.

Did the patient have pyelonephritis or tuberculosis of the urinary tract? Restricted fluid intake, alkali therapy and exacerbation of urinary-tract infection are all factors that might have correlated a flare-up of renal disease with a flare-up of his ulcer symptoms. Frequency, burning and nocturia all point to the bladder and were certainly marked features of his symptomatology previous to admission. Whether he had chronic Bright's disease or pyelonephritis secondary to intravesicular obstruction we do not know from the evidence. When he came in, vital signs were normal and the chemical studies were essentially normal, but he had a low phenolsulfonphthalein excretion — it was 33 per cent in two hours. So this man's many years of renal difficulty had left him with definite impairment of renal function. The specific gravity of 1.015 is of possible interest — since he came in with vomiting and was mildly dehydrated. What was the red-cell count?

*Surreon-12-Chief, Peter Bent Brigham Hospital

count was 6800. The urine showed a specific gravity of 1.015 and was normal.

A roentgenogram of the chest revealed some evidence of emphysema and fibrosis. A gastrointestinal series showed a severe, constricting deformity of the duodenal cap within which an ulcer crater could be seen. An intravenous pyelogram disclosed slight blunting and rounding of the calyces on the right as well as slight dilatation of the pelvis.

Cystoscopy performed six days after admission demonstrated normal bladder mucosa except for many small pieces of fibrin. Both ureters were easily viewed. The right ureter discharged small pieces of fibrin. The retrograde pyelogram showed some pelvic sacculation, but the calyces appeared sharp. After the cystoscope had been passed a large amount of cloudy urine was obtained, especially in the final dregs. A culture taken at the time of cystoscopy was later reported as showing no growth.

After cystoscopy the patient was noted to have difficulty in voiding. This symptom persisted. On the second day following cystoscopy he was given 2 gm of sodium sulfadiazine in 1500 cc of 10 per cent dextrose and water. On the next day a closed bladder drainage was established. The phenol-sulfonphthalein test at this time showed 18 per cent excretion of the dye in fifteen minutes and 50 per cent excretion at the end of two hours. On the following day he was found to have a temperature of 103°F (it had previously been normal). Examination of the urine revealed a +++ test for albumin, and the sediment contained 40 to 60 white blood cells and 20 to 30 red blood cells per high-power field. A urine smear showed scattered gram-negative rods and abundant colon bacilli. The white-cell count was 11,000. The nonprotein nitrogen was 29 mg per 100 cc. The daily dose of 2 gm of sulfadiazine had been continued, and twenty-four hours later the temperature was normal and remained there. Three days later a subtotal gastrectomy was performed. His postoperative condition was considered good. A subsequent pathological report disclosed a healing duodenal ulcer.

On the third postoperative day the urine was loaded with white blood cells, and a culture was positive for *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*). The temperature was normal, however. The nonprotein nitrogen was 26 mg, and the total protein 5.9 gm per 100 cc, and the chloride 98 milliequiv per liter. He was continued on 2.5 gm

of sodium sulfadiazine daily. Ten days after operation he was ambulatory, and he was taking a six-meal bland diet without difficulty. A blood sulfadiazine level was found to be 12.5 mg per 100 cc, after which the dose was reduced to 0.5 gm daily. On the following day, after a severe chill, the temperature rose to 103°F. He had difficulty voiding and complained of slight burning. There was no costovertebral-angle tenderness. The urine was loaded with white blood cells and bacteria. A gastrointestinal series showed some delay in the passage of barium at the gastric cardia. He was started on penicillin and streptomycin. During the next twenty hours the urinary output was about 250 cc. The temperature had remained at 103°F, and the white-cell count was 19,200. At this time the patient appeared very toxic. His face was flushed, and there was mottled cyanosis of the skin of the trunk and extremities. Respirations were rapid, and the pulse was 110. The blood pressure was 68 systolic, 40 diastolic. There seemed to be some spasm and tenderness in the right upper quadrant. The abdomen had a doughy feeling. Slight right-costovertebral-angle tenderness was also noted. An abdominal paracentesis later the same day produced only 5 cc of cloudy, nonodorous fluid. A smear showed many white cells. A culture was later reported to have grown nonhemolytic streptococcus and a questionable beta-hemolytic streptococcus. In an eleven-hour period following this the urinary output was about 30 cc. Examination revealed a +++ test for albumin, and the sediment contained countless white blood cells and red blood cells, but no crystals. (The urine became grossly bloody.) Study of the blood disclosed a nonprotein nitrogen of 67 mg and a total protein of 4.7 gm per 100 cc, a chloride of 83 milliequiv and a carbon dioxide of 14.6 milliequiv per liter and an amylase of 31 units and a sulfadiazine level of 8 mg per 100 cc.

In an effort to restore the electrolyte balance he was given hypertonic saline solution following which his condition seemed to improve. However, later the same day he complained of episodes of severe abdominal pain, recurrent in nature, with pain-free periods in between. The abdomen was rigid, silent and tender. The white-cell count was 15,400, and the temperature 101°F. A blood culture was later reported as positive for *B. pyocyaneus*.

On the following day he seemed considerably improved although he remained oliguric. The abdomen

be The blood sulfadiazine level was 12.5 mg per 100 cc, and along with 250 cc of urine a day there is no question that he was running a real risk of precipitation of this drug in the kidneys. The patient began to look toxic, and the blood pressure dropped. A flushed face and a high temperature may be due to kidney disease, but the mottled cyanosis and the blood-pressure drop are, in my experience, less commonly associated with an exacerbation of pyelonephritis. There seems to have been spasm in the right upper quadrant — something beginning to develop in the abdomen — despite the fact that it was twelve days after operation. Then toxemia developed, and there was a doughy feeling in the abdomen, and some distention — a characteristic finding in tuberculous peritonitis. The abdominal tap yielded only 5 cc of white, malodorous fluid. I wondered why they used the word "only." I would put an exclamation mark after this because it is difficult to obtain much fluid by tap. Usually with localization it is walled off, it is difficult to get much material by aspiration of a peritonitis.

Then the urinary output dropped even more — 30 cc in eleven hours. The urine became grossly bloody for the first time, and the blood chemical findings markedly abnormal. The nonprotein nitrogen was 67 mg per 100 cc, and the total protein dropped to levels that in the laboratories of this hospital are definitely compatible with an accumulation of edema. The chloride was 83 milliequiv, and the carbon dioxide 14.6 milliequiv per liter — in other words, total anions were depressed, with definite acidosis. I would just assume that the sodium was also very low. What was the sodium?

DR STANBURY: About 115 milliequiv per liter.

DR MOORE: The sulfadiazine level got down to 8.0 mg per 100 cc after the dose had been reduced to 0.5 gm. Did he have sulfonamide crystals in the urine? An effort was made to restore the chloride with saline solution. The situation was ripe for such therapy: plasma chloride is responsive to the use of hypertonic solutions. He developed more pain, recurring at intervals and suggesting smooth-muscle cramps. The blood culture was positive for *B. pyocyaneus*. I do not know how to interpret that, I doubt if it was the organism in his blood. The change from 115 to 128 milliequiv per liter in the blood sodium was due presumably to the concentrated saline solution.

Were the oliguria and anuria due to pyelonephritis from an ascending infection? Ulcer patients form stones and pass them from time to time, and this might have been the background. As a matter of fact 4 or 5 per cent of patients who come to surgery for duodenal ulcer will have a history of having passed renal stones. This patient did not, but that would be a logical background for pyelonephritis in this case. As far as the abdomen is concerned, the most likely bet is that he developed an abscess around the duodenal stump. This development was masked by sulfonamide, penicillin and streptomycin therapy. Toward the end of the history the abscess got larger, and we might hypothesize that it ruptured into the general peritoneal cavity — general peritonitis and obstruction. A great many things are against that duodenal-stump difficulty after ten days of apparently uneventful convalescence is rare. That brings it up to the second possibility, that he did not have peritonitis but that the malodorous abdominal fluid was a case of mistaken identity. The needle might have got into some viscus, possibly the bladder. His signs and symptoms may have been due entirely to renal disease. Ileus, cramps and distention can be seen not only in renal colic but also in kidney failure. The third possibility is that the abdominal picture and the renal disease were both on the same basis, and the only way I can tie them together is by the diagnosis of tuberculosis. If this patient had renal tuberculosis, we might assign it as the cause of the urinary symptoms and suggest that after a subtotal gastrectomy, for some reason, he developed tuberculous peritonitis.

We have three sets of diagnoses, and which shall I take? The safest bet is to take the commonest, although that is not the most intriguing possibility, and say that he had pyelonephritis, with renal failure, probably on the basis of stones, possibly made worse by the precipitation of sulfonamide in the kidney, and to account for the abdominal symptoms, a leak at the duodenal stump with the development of an abscess. Having taken what I think is the best bet, I shall hand Dr. Mallory an apple.

DR STANBURY: I saw this man two days before operation. At that time the problem as outlined was mainly one of renal failure, sepsis and disturbed electrolyte balance.

DR MALLORY No red-cell count is given

DR MOORE The total protein was 6.6 gm per 100 cc — suggestive of dehydration in a thin, depleted man. He should have been able to concentrate better than 1.015.

Let us have a look at all three sets of x-ray films at one time.

DR STANLEY M. WYMAN The films of the chest show no demonstrable gross abnormality. One film taken from the intravenous-pyelogram examination is poor because of the large amount of overlying gas in the large bowel. However, one can see that at fifteen minutes the contrast substance appeared in good concentration in both kidney pelves and calyces. Other films taken at this examination are less satisfactory. The pelvis of the right kidney is definitely somewhat wide, and the major calyces are wide. The minor calyces are not adequately seen, but I can demonstrate no gross blunting or lack of cupping. It is interesting that the bladder shadow is distended at this time, and as yet no dye has appeared in the bladder. The retrograde pyelogram done four days later again shows the rather large bladder, which may be a result of cystoscopy. I believe the pelves and major calyces are slightly widened on the right and perhaps even a little on the left.

DR MOORE Would you describe the kidney findings as compatible with a diagnosis of tuberculosis of the upper urinary tract?

DR WYMAN I do not think the evidence for tuberculosis is here unless it is in one minor calyx at the lower pole of the right kidney, which shows a narrow band of constriction. I can see this on no other film. It may be a chance result of muscle contraction at this time. I would hesitate to make a diagnosis of tuberculosis on the films available.

DR MOORE The course of the ureter does not seem abnormal?

DR WYMAN The course is normal, the ureter is a little bit wide. It is interesting that with withdrawal of the catheter from the left kidney there was a suggestion of blunting in the lower pole, which raises the question of an aberrant vessel or possibly, and less likely, a stricture. The gastrointestinal series before operation demonstrates the duodenal cap with a crater. The film taken after subtotal gastrectomy shows the gastric remnant and anastomosis of the jejunum.

DR MOORE What about the cystoscopy? I have already brought out that we cannot blame the urinary disease on cystoscopy. It antedated it since small pieces of fibrin were coming out of the right ureter. All that means is that the inflammatory process was above the bladder.

Then we move on to the institution of sulfadiazine therapy, which comes along through the rest of the history. There are two or three things of interest about it. Here is a patient with kidney disease (although at the time it was not certain how serious a factor it was going to become) who was given a drug that in the presence of oliguria might well have precipitated in the kidney. We should like to know if there were any casts in the sediment. Yet the nonprotein nitrogen stayed down, and the sulfadiazine was continued. I can well imagine the thoughts on the Surgical Service: Should they go ahead or wait? He was not taking oral feeding. Parenteral alimentation could not replace oral feeding indefinitely, and the surgeon probably wanted to get him over to oral intake. The temptation to open his alimentary canal was overwhelming, and despite the risk of gastrectomy they decided to go ahead with operation.

At first the patient did well. The temperature was normal. "He was continued with 2.5 gm of sulfadiazine." Was that by mouth or by vein?

DR JOHN B. STANBURY Both.

DR MOORE That is important. In a patient given sulfadiazine orally, after subtotal gastrectomy one cannot be confident of the degree of absorption in the postoperative period. But if the drug is given by vein, it gets into the body fluids and, therefore, is capable of producing difficulty in the kidneys. It is interesting that ten days after operation he was up and around, getting 2.5 gm a day, 2.5 gm is not a large dose, but the blood sulfadiazine level was 12.5 mg per 100 cc. That must have disturbed the Service, since he was not excreting the drug properly even with a small dose. Whereupon the temperature went up, apparently because of urinary difficulty. The urine sediment continued to be loaded with white cells and bacteria. A gastrointestinal series was taken and he was started on penicillin and streptomycin. This is interesting because this combined therapy is capable of masking a great deal that is going on in the abdomen. The urinary output was only 250 cc, approximately a fifth of what the Service would have liked it to

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"LEARNED ART AND PUBLIC SERVICE"

ROSCOE POUND in his address delivered at the annual dinner of the Massachusetts Medical Society in May and published as the leading article in this issue of the *Journal* describes clearly the position of the professions in the society of today.

Popular ideas of a profession are somewhat confused by the modern meaning of professionalism in its relation to athletics. Preferable to the concept of professional as used in apposition to amateur is that of a profession consisting of "a group of men pursuing a common calling as a learned art and as a public service."

A heritage of the Middle Ages, this pattern is the one in which medicine, the law, the ministry and teaching have developed and achieved their stature. Other important callings have come in recent years to be considered among the professions, being of much the same substance, "as learned arts,

taught in universities and pursued in a tradition of learning." Such are journalism, engineering, business administration, social work and public administration.

For many the idea of ethics helps to distinguish the profession, since ethics is implicit in its pursuit—not that a trade cannot and should not be ethically conducted, but its primary object is commercial. Three ideas, according to Dean Pound, are essential in a profession: organization, learning and the spirit of public service—to which he later adds a code of ethics. The earning of a living in a profession does not detract from its concept but may be curbed by the professional spirit.

This also is implicit in professional organization, that professional societies and associations exist only for the purpose of protecting and improving the standards of service, not for the benefit of the persons practicing the profession. If benefit accrues to the practicing personnel it follows naturally on an improvement in the quality and the conditions of the practice.

In America, Dean Pound points out the pioneer forefathers distrusted specialists in any line and put their faith in the versatility that had been so essential to their own success. This was to the detriment of the professions. Deprofessionalization was part of the creed of the frontier, which has made necessary a reprofessionalization during the last two generations.

The world moves on. As American political thought breaks away from its fear of governmental oppression of the individual, new pressures are appearing. From four sources in today's society the professional ideal is being threatened. These are the exigencies of the individual economic existence, which is always present, the increase in detail in every branch of learning, leading of necessity to partnerships and groupings, the pressure of business methods, and eventually the advent of the service state and "the growing tendency to rely on official rather than on individual private initiative and to commit all things to bureaus of politically organized society."

Here is the great menace to the professional ideal—"the development of great government bureaus and a movement to take over the arts prac-

DR MOORE Two days before the final operation?

DR STANBURY Yes From the chart, as we saw it, it seemed obscure About forty-eight hours before the final operation, he really began to get into trouble He was up and about during that time, and we have no way of knowing whether the sulfonamide was being precipitated

DR MOORE Do you see renal difficulty due to precipitation of sulfonamides in the kidney tubules without any crystals coming down into the urine?

DR STANBURY Usually we see the crystals

DR MOORE Lower-nephron nephrosis after transfusion without hemoglobinuria?

DR MALLORY I would say almost certainly no to both questions

DR ALLAN M BUTLER Sulfonamide reaction can occur in the absence of crystals in the urine

DR STANBURY We were concerned with the electrolyte balance Dr Jack Crawford helped us on that The patient was moribund, and Dr Crawford brewed us a solution of hypertonic saline and lactate, which was given every two hours with dramatic improvement The cyanosis disappeared, the respirations improved, and the patient looked better

DR MOORE Did the renal output improve after the hypertonic infusion?

DR STANBURY Not appreciably

DR BUTLER Did the blood pressure improve?

DR STANBURY Yes We thought along with the surgeons that he had sepsis in the right upper quadrant

CLINICAL DIAGNOSES

Pyelonephritis, *B pyocyaneus*

Peritonitis, acute

Septicemia, *B pyocyaneus*

DR MOORE'S DIAGNOSES

Pyelonephritis with renal failure, caused by renal stones and possibly sulfonamide nephrosis

Abdominal abscess at site of gastrectomy

ANATOMICAL DIAGNOSES

Pyelonephritis, severe, *B pyocyaneus*

Operation subtotal gastric resection for duodenal ulcer

PATHOLOGICAL DISCUSSION

DR MALLORY At the time of exploration no gross peritonitis could be found and no evidence of any localized sepsis The patient died shortly after operation

DR MOORE Did he have anything at that exploration to correlate with the 5 cc of purulent fluid?

DR MALLORY A small amount of slightly cloudy fluid was found, nothing else At autopsy our findings were similar The peritoneum contained a slight amount of fluid, a little old fibrin and no evidence of acute peritoneal reaction and no localized sepsis The stomach and the resection lines in the stump of the duodenum were perfectly adequate Our only important finding at autopsy was in the kidneys, which showed extremely severe, extensive pyelonephritis Cultures from them showed a pure culture of *B pyocyaneus* I think the finding of *B pyocyaneus* in the blood stream ante mortem was unquestionably due to septicemia It is an organism of low virulence and on frequent occasions has been observed to go with septicemia We did not find any other organisms in the kidneys It was not possible, in the face of severe, acute reaction in the kidneys, to say with any definiteness whether there was longstanding pre-existing pyelonephritis Everything was obscured by the intense reaction, and the renal substance consisted almost entirely of a mass of focal abscesses There were a few old calcium spicules scattered here and there in the renal parenchyma, which probably went back to the alkali therapy

DR MOORE It might be worth while to say that the hunch, that the ten-day period of convalescence really did have significance, was correct I think that is an important point

DR MALLORY Yes

Report in its entirety — that a wedge has been driven in that will split the recommendations of the Commission from stem to stern

Such an interpretation, however, need not be given major consideration. The Commission itself was by no means emphatically in favor of the department of welfare and gave at least partial support to the idea of a separate department of health. The argument of the proponents of the plan, that the Administration's proposals should have been accepted at the time and corrected later if necessary, by the separation of the department into those units that would function best independently of each other, presented a species of reasoning that scarcely needed to be taken seriously. Eggs are not thus easily unscrambled, nor can an ambitious department head, should such a one be chosen, be expected to give up any part of his authority without a struggle.

A POOR SHOWING

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There are various reasons for this absolute and relative delinquency. A number of the fellows of the Society are financially unable to meet the assessment, and no pressure is being put upon them to pay. The Society does not ask any fellow to assume an undue burden on this account. With many, however, it is believed to be a matter of principle, real or apparent, that although they are opposed to compulsory federal health insurance, they are even more opposed to the methods of the American Medical Association in combating it and will have no part in such an undertaking.

These physicians are urged to see the problem as a whole, one in which they are all involved, and one in which minor grievances and criticisms of methods

should not stand in the way of the larger principles at stake. Such a plea is not directed to those few doctors who are honestly and earnestly in favor of compulsion. Their principles are respected as all honest principles should be. Otherwise the situation appears to be one in which an association of physicians in need of funds, levies an assessment on its membership, as provided in its by-laws. Approximately half the members from one state, still retaining their membership, neglect to pay.

There are times when Massachusetts may well be proud to stand with a courageous minority instead of with a mistaken majority. Is there any evidence that this is one of them?

A physician from Westchester, N Y, has established himself on the banks of the Sacramento, in a log cabin, one-half of which he uses as a store and the other as a hospital, and it is said that he receives as much gold daily as the average of twenty miners.

Boston M & S J, September 5, 1949

MASSACHUSETTS MEDICAL SOCIETY



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It is hoped that personal contacts in the various districts will bring the desired result.

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"The service state," Dean Pound is willing to concede, "is a political step forward. But we must not let it turn back upon itself and lead us to absolutism. There is no surer road to absolutism than an unchecked omniscient bureaucracy."

Freedom is not a natural state for man, which rushes in wherever a political vacuum exists. It must be fought for, cherished and guarded, against threats from within as well as from without. It is based on tolerance, which is one of the rarest social and political attributes. Nowhere has true democracy, now in jeopardy, been more subtly defined than in a quotation from the essayist, E. B. White, published in the *Harvard Alumni Bulletin*:

"Democracy," according to this definition, "is the recurrent suspicion that more than half of the people are right more than half of the time."

HEALTH UNIT BILL BECOMES LAW

THE Union Health Bill, enabling all towns and cities of Massachusetts to form union health departments, was signed by Governor Dever on August 10. Such combinations at a community level actually add strength to decentralization in government, long a New England tradition but unique in present political procedures.

The Commonwealth of Massachusetts entered early the field of public health with the establishment of the first board of health in Boston in 1799. Seventy years later the first state department of health in the country was established in Massachusetts, a delayed result of Lemuel Shattuck's famous survey. This early entry into the field gave rise, however, to the acceptance of methods and traditions that, though outworn, have survived to the present day. Systems of organization that were suited to the relative isolation of communities and

the slow rate of travel of another century are not adapted to cope with the increased populations and the mobility of today.

Under the circumstances that at present prevail, each of the 351 cities and towns of the Commonwealth has its own board of health, with no health officer at all in 113. Only a few communities have joined forces in providing a better grade of public-health services for themselves, as has been done through the Nashoba Health Unit. The new law, called by Dr. Vlado A. Getting, commissioner of public health of Massachusetts, "the most important health legislation that has been passed since the establishment of our State Department of Health in 1869," removes the barriers that have prevented the people of Massachusetts from having all the available advantages of public-health protection.

The Act makes possible the formation generally of units such as that which exists in the Nashoba area, headed by full-time medical directors chosen by the union boards of health. The need was emphasized in the 1948 Recess Commission Report to the Massachusetts General Court, which recommended full-time union health departments for each 35,000 population group in the State.

Through these units the advantages of immunization of pre-school children, pre-natal advice to mothers, well-child conferences, inspection of private water supply and sewage systems, chest x-ray examination and the control of communicable disease can be brought to the people of the Commonwealth wherever they may live.

Through better health services for all the people will come one of their best defenses against the extension of sickness taxation at any level.

DEFEAT OF PLAN 1

THE rejection by the United States Senate last month of Reorganization Plan 1, the proposal for an all-inclusive department of welfare, has resulted in considerable lamentation and some recrimination from friends and foes of the Administration alike. The most serious criticism of the Senate vote and the most apparently logical one appears to be that the rejection of this initial fractional reorganization plan represents a potential rejection of the Hoover

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The highest prevalence so far has been in the Boston metropolitan area and toward the north shore

The incidence of measles was the lowest in forty years. Scarlet fever was at the lowest level ever recorded for July

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Beverly, 1, Boston, 14, Chelsea, 2, Danvers, 1, Leominster, 2, Malden, 3, Medford, 1 total, 24

Dysentery, bacillary, was reported from Boston, 1, total, 1
Encephalitis, infectious, was reported from Swansea, 1 total, 1

Infectious hepatitis was reported from Cambridge, 1, Springfield, 1, Wrentham, 1, total, 3

Malaria was reported from Haverhill, 1, total, 1
Meningitis, meningococcal was reported from Boston, 1, Easthampton, 1, Salem, 2, Waltham, 1, total, 5

Meningitis, Pfeiffer bacillus, was reported from Falmouth, 1, Springfield, 1, total, 2

Poliomyelitis was reported from Agawam, 1, Arlington, 2, Beverly, 1, Billerica, 1, Boston, 18, Brockton, 5, Brookline, 1, Cambridge, 7, Chelsea, 2, Dedham, 1, East Longmeadow, 1, Everett, 1, Falmouth, 1, Haverhill, 1, Lynn, 8, Malden, 1, Marlboro, 1, Medford, 2, Melrose, 3, Milton, 1, Natick, 1, Newton, 1, North Attleboro, 2, North Reading, 2, Plymouth, 1, Quincy, 1, Revere, 2, Salem, 1, Salisbury, 1, Saugus, 1, Sharon, 1, Somerville, 6, Springfield, 2, Stoneham, 1, Waltham, 1, Wareham, 1, Watertown, 3, Wellesley, 1, Westwood, 1, Weymouth, 1, Wilmington, 1, Winchester, 1, Worcester, 1, total, 93

Salmonellosis was reported from Boston, 3, Plymouth, 1, Waltham, 1, total, 5

Septic sore throat was reported from Boston, 4, Lowell, 1, Lynn, 2, total, 7

Tetanus was reported from Taunton, 1, total, 1
Typhoid fever was reported from Boston, 2, Leominster, 1, Winthrop, 1, Worcester, 3, total, 7

Undulant fever was reported from Boston, 1, Douglas, 1, Medway, 1, New Marlboro, 1, total, 4

MISCELLANY

ANGIOLOGY

Angiology, The Journal of Peripheral Vascular Diseases, will begin publication in February, 1950. Dr. Saul S. Samuels, chief of the Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic, New York City, will be editor-in-chief. Among the associate editors in the United States will be Dr. Alton Ochsner, of Tulane University; Dr. Keith Grimson, of Duke University; Dr. Leo Loewe, of Long Island Medical College; Dr. D. W. Kramer, of Jefferson Medical College; and Dr. Gerald Pratt, of New York University Medical School.

The new journal will be published by the Williams and Wilkins Company, of Baltimore.

CORRESPONDENCE

JARISH-HERXHEIMER REACTION QUESTIONED

To the Editor: There is considerable question in my mind concerning the case report by Dr. Diefenbach in the July 21 issue of the *Journal*, entitled "Fatal Jarish-Herxheimer Reaction with Sudden Aneurysmal Dilatation and Complete Bronchial Occlusion Following Penicillin Therapy." There is no question that the patient died of bronchial obstruction fifty-seven days after the institution of therapy, but whether the penicillin therapy had any causal relation remains unproved; it seems to me Jarish-Herxheimer reactions usually occur within the first twenty-four to forty-eight hours, and there usually is associated fever, which was absent in this case after the institution of penicillin.

I am a little disappointed to see the *New England Journal of Medicine* publish a report about which, there seems to me, to be so much question.

JAMES H. CURRENS, M.D.

Boston

Dr. Currens's letter was submitted to Dr. Diefenbach who offers the following reply:

Penicillin therapy was instituted late on the first hospital day and x-ray study of the chest showed a clear left-lung field. Thirty-six hours after the administration of penicillin there was sudden dyspnea with all signs of complete obstruction of the left main bronchus, confirmed by bronchoscopy and roentgenogram.

Although it is true that the patient did not expire immediately the fact remains that a Jarish-Herxheimer reaction had occurred and that he subsequently died of a suppurative pneumonia.

WILLIAM C. L. DIEFENBACH, M.D.
Englewood, New Jersey

BOOK REVIEWS

Child Health Services and Pediatric Education. Report of the Committee for the Study of Child Health Services. The American Academy of Pediatrics. With the co-operation of the United States Public Health Service and the United States Children's Bureau. 8°, cloth, 270 pp. New York: The Commonwealth Fund, 1949. \$3.50.

The Committee for the Study of Child Health Services of the American Academy of Pediatrics has recently completed a three-year nationwide survey of the services and facilities available for the medical care and health supervision of infants and children. This survey included also a study of the training in pediatrics that the physicians who provided this care had received both general practitioners and pediatricians, and the opportunities for education in this field now offered by medical schools and hospitals. The book gives the findings of this survey in summary and graphic forms and the Committee's interpretation of these findings. A supplemental report, *Methodology and Tabulations on Services*, also published by the Commonwealth Fund, will be released shortly for those who wish to study the data in greater detail. These two volumes constitute the final report of this national committee and of the survey on a nationwide basis.

This study was initiated by and conducted throughout under the leadership and direction of the American Academy of Pediatrics, its representative, Dr. John P. Hubbard, serving as director. It was carried out with the technical aid and full co-operation of the United States Public Health Service and the United States Children's Bureau. Without the able assistance of Dr. Katherine Bain, of the Children's Bureau, and Mr. Rollo Britten and Mrs. Maryland Pennell, of the United States Public Health Service, this report would not have been possible. The Committee and its large staff were also aided by many national, state and local groups concerned with the care of children, as well as by a large number of practicing physicians, dentists and other persons, who made the required information available. It was accomplished at a cost of \$1,000,000 provided collectively by several foundations and commercial houses, as well as by the American Academy of Pediatrics and the National Institute of Health. This is the first time that a comprehensive study of medical services to children has been made in the United States, and it is gratifying that it has been done by the national organization of physicians best qualified to deal with the health problems of children. It is of interest that this organization was able to obtain the very general co-operation of the practicing physicians of the country and that it received at its own request extensive assistance from two governmental agencies equipped through national experience and statistical facilities to meet many of the basic needs for such a project.

Massachusetts physicians have been well represented among the leaders of this project of the Academy at the national level. Dr. Warren Sisson served as chairman of the National Committee, and Dr. John Hubbard, its executive secretary, was in charge of its large staff in Washington. Dr. Lendon Snedeker acted during the survey as regional representative of the central office and now is executive secretary to the Massachusetts Committee, which is preparing the report for this state. Dr. James Wilson is chairman of the Committee for the Improvement of Child Health Services. All of these are now or were formerly Boston pediatricians. The Committee for the Study of Child Health Services now has completed its authorized undertaking, and the Committee for the Improvement of Child Health Services will for-

DEATHS

Boos — William F. Boos, M.D., of Fall River, died on August 11. He was in his eightieth year.

Dr. Boos received his degree from Harvard Medical School in 1901. He was medicolegal expert for the federal Government and the Commonwealth of Massachusetts and for many years was toxicologist for the Suffolk County medical examiner. He was a fellow of the American Medical Association.

His widow and two daughters survive.

Dunn — William A. Dunn, M.D., of Boston, died on July 15. He was in his eighty-first year.

Dr. Dunn received his degree from New York University Medical College in 1893. He was formerly police surgeon and physician at the Boston prison and House of Detention. For twenty-five years he served as assistant to the medical examiner of Suffolk County.

Emery — William C. Emery, M.D., of Dorchester, died on August 20. He was in his seventy-sixth year.

Dr. Emery received his degree from Harvard Medical School in 1909. He was a fellow of the American Medical Association.

His widow and two sons survive.

Reagh — Arthur L. Reagh, M.D., of West Roxbury, died on June 15. He was in his seventy-ninth year.

Dr. Reagh received his degree from Harvard Medical School in 1898.

Robinson — Henry A. Robinson, M.D., of Hingham, died on August 21. He was in his third year.

Dr. Robinson received his degree from Harvard Medical School in 1911. He was a member of the New England Pediatric Society.

His widow, a daughter, his father and a brother survive.

Story — Theodore L. Story, M.D., of Southbridge, died August 9. He was in his sixty-second year.

Dr. Story received his degree from Tufts College Medical School in 1917. He was a fellow of the American Medical Association.

His widow, a brother and two grandchildren survive.

Tierney — Thomas F. Tierney, M.D., of Hudson, died July 24. He was in his seventy-third year.

Dr. Tierney received his degree from Baltimore Medical College in 1901. He was a fellow of the American Medical Association.

Two sons, a daughter and a brother survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NITRITE POISONING IN INFANTS

From various places in the country come reports of acute illnesses, mostly in young children or infants, that have been traced to drinking of waters high in nitrates. The illness is marked by a blue color of the skin with rapid recovery when the source of water is changed. Unless properly diagnosed and treated, however, the disease is by no means to be lightly regarded. Some reports indicate a mortality of 10 per cent.

The apparent explanation for the difficulty lies in the young infant's inability to break down satisfactorily the nitrates into ammonia. The resultant nitrites combine with hemoglobin to form methemoglobin.

Arthur D. Weston, C.E., director of the Division of Sanitary Engineering, Massachusetts Department of Public Health, has investigated Massachusetts waters and reports that in recent years the highest yearly average nitrate content of any public water supply in the Commonwealth has in only one case exceeded 10 parts per million, a concentration believed to be the upper limit of safety. This was exceeded by the semi-public supply of Whately (Craft Springs) in 1943, 1944 and 1945, when it was found to be 17.1, 20.8 and 13.0 parts in a million, respectively.

Considerably higher nitrate content has been reported, however, in this state in waters of rural water supplies such as the "farm well."

No cases of methemoglobinemia have been reported thus far to the Department of Public Health as chargeable to water supplies in this state. Precise information is needed to disclose the minimum concentration of nitrates in waters that have actually caused cases of methemoglobinemia among infants.

The Massachusetts Department of Public Health would welcome notification by physicians of any cases of methemoglobinemia. The Department will arrange for examination and analysis of water used in connection with the feeding of these infants.

PREVALENCE OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1949

DISEASE	RÉSUMÉ		
	JULY 1949	JULY 1948	SEVEN YEAR MEDIAN
Chancroid	3	4	2 ^a
Chicken pox	490	619	516
Diphtheria	24	14	14
Dog bite	1270	1497	1229
Dysentery bacillary	1	9	9
German measles	121	61	62
Gonorrhea	257	284	356
Granuloma inguinale	0	0	1 ^a
Lymphogranuloma venereum	0	0	15
Malaria	1	4	1159
Measles	394	2461	13
Meningitis meningococcal	5	5	2
Meningitis, Pfeiffer bacillus	2	6	3
Meningitis, pneumococcal	0	3	0
Meningitis staphylococcal	0	0	0
Meningitis streptococcal	0	1	3
Meningitis undetermined	0	3	434
Mumps	442	787	11
Polomyelitis	93	9	11
Salmonellosis	5	2	263
Scarlet fever	91	269	321
Syphilis	140	225	256
Tuberculosis, pulmonary	259	251	17
Tuberculosis other forms	12	19	4
Typhoid fever	7	4	5
Undulant fever	4	5	551
Whooping cough	387	130	

*Five year median

COMMENT

Diseases above the seven-year median were diphtheria, dog bite, German measles, mumps, poliomyelitis, pulmonary tuberculosis and typhoid fever.

Diseases below the seven-year median were chicken pox, bacillary dysentery, malaria, measles, meningococcal meningitis, salmonellosis, scarlet fever, undulant fever and whooping cough.

Diphtheria was still unusually prevalent for this time of year. Although the incidence of German measles and mumps was higher than the seven-year median, both diseases occurred much less often than in the previous month.

The incidence of poliomyelitis reported for the month of July was the highest it has been in the last three decades.

Writing as a lover of the Italian land and people, the author has correlated with data from the classics some of the information that he has gathered during years of acquaintance with many parts of the Italian peninsula and of Sicily, and from a lifetime of reading in the voluminous literature in various languages about their inhabitants. But his comparison of two widely separated periods of that people's history is more than "a loving likelihood," for he finds not only that many pagan practices and superstitions persist in combination with Christian custom but also that identical beliefs, charms, drugs, exorcisms, herbs, incantations, spells and talismans that were employed by Romans twenty centuries ago are still used among their peasant descendants of today. Even the Phi Beta Kappa key has been mistaken as some sort of American amulet. Much folk medicine is based on sympathetic magic, on the familiar principle of *similia similibus curantur*.

This volume, which is abundantly documented by a bibliography of 350 references to classical and modern literature, is an invaluable treasury of interest to gynecologists, obstetricians and pediatricians, as well as to students of the classics and of folklore and folkways. It is a humanistic work of well directed research and of profound scholarship.

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mulate recommendations designed to correct the deficiencies described in the present report.

This book provides a welcome opportunity to shift the base of discussions of medical needs from broad, undocumented generalizations to sound data applicable to the situations under consideration. Upon such facts alone can a satisfactory program for the improvement of child care be constructed, and the Academy may be justly proud of its leadership in obtaining them. It is unfortunate that comparable information respecting the medical care of other age groups has not been assembled under the leadership of the medical profession so that all discussions of medical care could be approached in the same way.

A unique feature of this report is its excellent condensation and presentation of a large number of data. The charts are expertly constructed to reveal the essential facts, unnecessary tables and statistical compilations have been strictly eliminated. The text is also brief and readable and well correlated with the charts, highlighting them without undue repetition. As a result, the reader is hardly aware of the enormous number of statistical analyses dealt with.

The report is presented in three parts: child health services, pediatric education, and a general summary. In the first part the introductory statements about the technical aspects of the study itself are commendably brief, and the summaries of findings by region, race, density of population, age and economic group begin to occupy the reader's attention in the first chapter. These summaries include data on births, deaths, hospital facilities and amounts of medical, dental and other health services available for each group considered. They show that children in or near cities receive far more medical care, more specialists' services and better hospital and clinic facilities than children living away from cities. They show, furthermore, that community health services do not fill the gaps in medical care for those unable to obtain it privately. For example, 2000 counties in the United States, representing 31 per cent of the children under five years of age, have no well-child conference for those unable to obtain health supervision otherwise. Only 6 per cent of the children in the country as a whole attend such conferences. Health services for school children are found to be almost as inadequate. Variations between the states and their local subdivisions in amounts and kinds of services generally are tremendous.

The second part of the report gives an excellent picture of the extent of training or, more properly, the inadequacies of training in pediatric subjects provided in connection both with undergraduate medical education and with graduate education in hospitals. It shows clearly that present educational facilities do not provide general practitioners the training in child care that they require. Almost half the general practitioners have had little hospital training in pediatrics, and yet three quarters of the private care of children is in their hands.

The character and the extent of the deficiencies in medical care and health services for children throughout the United States and in pediatric education have been clearly revealed by this over-all report. A brief review of the findings in their broad perspective is presented in the third part, which focuses attention on the principal deficiencies. Each of the New England states may determine from this national report its standing among the states and comparable communities in the availability to children of the various services studied and to some extent their quality. The supplementary volume referred to will give more of the crude data for further use by those concerned with development of plans, and the data themselves have been returned to each state and are available to local agencies for further study.

It is not possible in this review to summarize for all types of service the positions held by each New England state in relation to other states or to the national average. The regional summarizations in the report group the New England with the North Central states, and the average ratings for this group of very dissimilar communities are not very informative concerning the situation in any one. The findings for these states are generally favorable in relation to most other regions, and, in some respects, they are outstanding. However, the individual New England states show sharp individual differences as well as local area differences by counties or health districts. Information was made available to Massachusetts on the basis of its public-health districts by special arrangement because the county data were not

found satisfactory for use in this state. Individual states in the New England area are to be found in the lowest as well as in the highest categories in some ratings—for example, that for infant mortality. So, also, a high state rating for a given service—for example, the number of physicians available per thousand children—may go hand in hand with the finding that certain communities within the state lack available physicians' services.

Among generally favorable circumstances in the New England states may be mentioned the following three of the states are in the highest category for number of hospital beds reserved for children. Some of these beds, obviously, are available to children from other states, which, in part because of this, maintain fewer beds for children. The children in all the New England states, except one, have more physicians available and receive more medical care generally and more hospital care specifically than the average for the country as a whole. Children in all these states are also relatively well provided with dental care. All these states exceed the national average in the percentage of births occurring in hospitals, Connecticut having the highest percentage for any state and Massachusetts holding fourth place. On the whole, the record for this region, as revealed by this study, is an excellent one. It offers the best available evidence of the advanced development of medical services in some of the New England states. As in the rest of the country, the local situations that are out of tune with this general picture appear to depend more upon the extent of urbanization of the area than upon state lines. This is particularly true of medical care and is less applicable to health services such as well-child conferences and public-health nursing services, which more clearly reflect state planning. The amount of the physician's time devoted to the various services for well children varies tremendously, being related in part at least to the number of physicians per unit of population.

Physicians will not all agree about the significance to the children concerned of some of the ratings assigned to their communities on the basis of the data obtained in the survey. They will all find it a stimulating undertaking, however, to look at the facts and to attempt to interpret them objectively. No one is better fitted to interpret the facts than the physicians in the community to which the specific ratings apply. The next step obviously is for each state and local community to study its own problems in the light of this revealing information, and all physicians concerned with the care of children will be interested in such an analysis. The progress that is made as a result of this study will depend in no small measure upon the extent to which physicians generally acquaint themselves with the facts, both from the national report and from the studies of local findings. The considered actions that they take individually and collectively to improve local situations will have much to do with the character and effectiveness of this progress.

Each state committee of the Academy is responsible for the report of the findings for its state and for recommendations based upon them. The state chairmen for New England are as follows: Maine, Dr Thomas A. Foster; New Hampshire, Dr Cohn C. Stewart, Jr.; Vermont, Dr Paul D. Clark; Massachusetts, Dr James M. Baty; Rhode Island, Dr William P. Buffum; and Connecticut, Dr J. Howard Root. Some state committees have already published reports, but others are still occupied with this large undertaking. The report for Massachusetts is nearing completion and will be available for general distribution early in the fall. Massachusetts is fortunate in having had other studies in progress during the past two or three years that supplement the Academy study and provide a far more adequate body of knowledge than is ordinarily available when a program for improvement of services is being developed.

Conception, Birth and Infancy in Ancient Rome and Modern Italy. By Walter B. McDaniel. 8°, cloth, 77 pp. Lancaster, Pennsylvania: Business Press, Incorporated, 1948.

This monograph, recently given by its author, a distinguished American classical scholar, to the Boston Medical Library, presents the result of his prolonged, painstaking observation and research in the fields of folk medicine and comparative literature. It is a study of the popular beliefs, practices and superstitions relating to conception, pregnancy, childbirth and infancy among the ancient Romans and among their heirs and racial descendants in modern Italy.

Writing as a lover of the Italian land and people, the author as correlated with data from the classics some of the information that he has gathered during years of acquaintance with many parts of the Italian peninsula and of Sicily and from a lifetime of reading in the voluminous literature in various languages about their inhabitants. But his comparison of two widely separated periods of that people's history is more than a loving likelihood, for he finds not only that many pagan practices and superstitions persist in combination with Christian custom but also that identical beliefs, charms, drugs, sorceries, herbs, incantations, spells and talismans that were employed by Romans twenty centuries ago are still used among their peasant descendants of today. Even the Phi Beta Kappa key has been mistaken as some sort of American amulet. Much folk medicine is based on sympathetic magic, on the familiar principle of *similia similibus curantur*.

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How To Live Longer By Justus J Schifferes With a foreword by Ralph F Sikes, M.D. 8°, cloth, 255 pp New York E P Dutton and Company, Incorporated, 1949 \$3.00

Mr Schifferes, formerly a teacher of health education and hygiene at Columbia University and Teachers College, organizer and director of the Health Education Council, co-founder of the periodical *Modern Medicine* and its editor for ten years, has written a popular manual on the prevention of the great common diseases of mankind. The volume is not a "home medical handbook", it does not diagnose illnesses or prescribe treatment. It endeavors to point out the warning signs in time for proper therapy to be instituted. The text is written in simple, nontechnical language and is based on the latest information on public health and on the latest United States Government statistics. It discusses the "Big Killers"—heart disease, cancer, stroke, kidney disease, accidents, pneumonia, tuberculosis, premature birth, diabetes, suicide and syphilis. The chapter entitled "Little Danger Signals" is very valuable and should be available to the entire population of the country. The final chapter comprises a list of health-promoting organizations and their publications. There is a good index. The type, printing and paper are excellent for this type of book, which should be in all public libraries and in the popular section of medical libraries.

Your Coughs, Colds and Wheezes By Joseph D Wassersug, M.D. 12°, cloth, 277 pp New York Wilfred Funk, Incorporated, 1949 \$2.95

In this book for the laity the author discusses the common cold, its prevention and treatment and the various respiratory diseases. Dr Wassersug is a competent authority on chest diseases and enjoys a wide experience in that field. The text is well written but seems a little too technical in certain places for the general reader.

NOTICES

ANNOUNCEMENT

Dr S Brodie announces the opening of his office for the practice of pediatrics at 238 North Main Street, Fall River, Massachusetts

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The sixth lecture will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Wednesday, September 28, at 8 p.m.

Dr William L Fleming will speak on the subject "Present Status of Penicillin Therapy in Syphilis."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will also be shown during this period.

SOCIETY MEETINGS AND CONFERENCES

- SEPTEMBER 13 New England Society of Anesthesiologists Page 130, issue of September 1
- SEPTEMBER 28 New England Pediatric Society Page 136, issue of July 21
- SEPTEMBER 28 94th Infantry Division Lecture Notice above
- SEPTEMBER 28-30 Mississippi Valley Medical Society Page 11, issue of July 14
- OCTOBER 3-MAY 19 Massachusetts Department of Mental Health Postgraduate Seminar in Neurology and Psychiatry Page 286, issue of August 18
- OCTOBER 11-15 American Society of Clinical Pathologists Drake Hotel Chicago
- OCTOBER 13 Mononucleosis Dr Andrew Contratto Pentucket Association of Physicians 8:30 p.m. Haverhill
- OCTOBER 24-26 National Gastroenterological Association Page 231, issue of August 11
- OCTOBER 24-28 American Public Health Association Page 251, issue of August 11
- NOVEMBER 2 New England Obstetrical and Gynecological Society Hotel Somerset Boston
- NOVEMBER 2-5 Pan American Congress of Pediatrics Page 251, issue of August 11
- NOVEMBER 3-5 American Association of Blood Banks Page 21, issue of June 16
- NOVEMBER 7-9 National Society for Crippled Children and Adults Page 184, issue of July 28
- NOVEMBER 7-12 International College of Surgeons Page 251, issue of August 11
- NOVEMBER 14-17 American Academy of Pediatrics Page 251, issue of August 11
- NOVEMBER 16 Massachusetts State Society of Examining Physicians Page 324, issue of August 25
- DECEMBER 28 AND 29 American Association for the Advancement of Science Page 350, issue of September 1
- FEBRUARY 20-23 American Academy of General Practice Page 254, issue of August 11
- JULY 17-22 International Congress for Scientific Research Page 214, issue of September 1

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 15

FRIDAY, SEPTEMBER 16

- *9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds, Peter Bent Brigham Hospital
- *12:00 p.m. X-Ray Conference, Margaret Jewett Hall, Mount Auburn Hospital, Cambridge
- *1:30 p.m. Tumor Clinic, Out Patient Department, Mount Auburn Hospital, Cambridge

MONDAY, SEPTEMBER 19

- *11:30 a.m.-12:15 p.m. Chest X-Ray Conference, South End Health Unit, 57 East Concord Street, Boston. Dr Cleveland Floyd in charge
- *12:15-1:15 p.m. Clinicopathological Conference, Main Amphitheater, Peter Bent Brigham Hospital

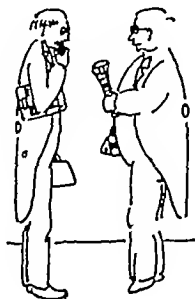
TUESDAY, SEPTEMBER 20

- *12:15-1:15 p.m. Clinicorontogenological Conference, Peter Bent Brigham Hospital
- *1:30-2:30 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital

WEDNESDAY, SEPTEMBER 21

- *12:00 p.m.-1:00 p.m. Clinical Conference (Children's Hospital), Amphitheater, Peter Bent Brigham Hospital

*Open to the medical profession



*Dr Wise, soundly trained and well read,
To a fellow practitioner said
Here's a word from the Wise—
Better firms advertise
In the New England Journal of Med*

The New England Journal of Medicine

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Volume 241

SEPTEMBER 15, 1949

Number 11

SPONTANEOUS PERFORATION OF THE ESOPHAGUS

Report of Three Cases Successfully Treated Surgically

JOSEPH P. LYNCH, M.D.*

BOSTON

SPONTANEOUS perforation of the presumably normal esophagus has been considered a rare lesion. A recent increase in the number of reports on this subject indicates that it may not be as unusual as was formerly believed. Barrett,¹ Olsen and Clagett² and Kinsella³ have recently considered this subject so completely that further review is unnecessary. The original, classic description of the lesion by Boerhaave in 1723 and the first diagnosis made during life by Walker⁴ in 1914 represent historical milestones. In modern times, the diagnosis has been made before death a number of times, but seldom early enough to permit treatment. Recent advances in thoracic surgery, as well as the development of the antibiotics, have made it possible to treat such patients successfully when the diagnosis is made early. Therefore, an awareness of this lesion and its characteristic symptomatology becomes increasingly important.

Spontaneous perforation differs from other types of perforation of the esophagus. In traumatic perforations the history of aspiration of a foreign body or a previous operative manipulation serve to focus attention on the esophagus. Occasionally, a peptic ulcer of the esophagus perforates and the history is similar to that of patients with spontaneous perforation. However, the history of previous symptoms of ulcer should make one suspicious of the underlying cause. Since the pre-existing ulcer usually sets up a reaction in the mediastinum, perforation is generally directly into the pleural cavity, with the formation of a hemothorax, an infrequent occurrence in spontaneous perforation of the esophagus.

In most of the cases of spontaneous perforation of the esophagus described in the literature, there has been no background in the history that would lead one to suspect disease of the esophagus. Furthermore, since most cases occur during vomiting there is immediate flooding of the mediastinum with

the highly irritant gastric contents. This gives rise to the characteristic symptoms usually noted, which are seldom present when the perforation is traumatic.

Commonly, the history is one of a patient vomiting for one of many reasons—most frequently after a bout of alcohol ingestion. In the course of vomiting, and usually after severe retching, there has been sudden severe pain, usually referred to the precordium or epigastrium or both. This pain is generally associated with a shock reaction, dyspnea and, at times, cyanosis. The physician first seeing the patient frequently considers coronary thrombosis the most likely diagnosis although including the possibility of a perforated gastric ulcer. The blood pressure is low, the pulse is rapid, the temperature is subnormal, and there may be upper abdominal tenderness and spasm. These signs usually continue for the first few hours after onset. The blood pressure gradually rises but generally remains at a lower than normal level. The temperature rises, and signs of a pleural effusion develop. This occurs almost always on the left but has occasionally developed on the right. Within six to twelve hours of onset, air may be palpable in the neck, and this, with the previous history, is diagnostic of perforation of the esophagus. From the history, one should always suspect the condition in any patient who has sudden severe epigastric or precordial pain that comes on during vomiting.

Since most patients are hospitalized almost immediately because of the severe nature of their illness, and since perforated ulcer is suspected, it is usual to have an x-ray examination of the abdomen in a search for subphrenic air. Such a procedure can be most helpful in the diagnosis, since air behind the heart is frequently seen and is one of the most characteristic findings. Even in the early stages, a small pleural effusion has been noted. The usual chest x-ray film at this time may also show air in the upper mediastinum. Under the circumstances here described, such a finding is diagnostic.

*Visiting surgeon for thoracic surgery, St. Elizabeth's Hospital and Massachusetts Memorial Hospitals; consultant in thoracic surgery, Carney Hospital.

Untreated, the course is progressively downhill, and the majority of patients have died within forty-eight hours of the onset of the lesion.¹ There are described in the literature 2 cases in which a localized empyema or mediastinal abscess developed, the perforation of the esophagus closed spontaneously, and recovery followed drainage of the empyema or mediastinal abscess.⁶ Such a localization must be rare, the usual outcome of esophageal perforation being one of diffuse mediastinal infection that is rapidly fatal. Attempts to drain the local infection by mediastinotomy or pleural drainage during the acute stage have generally been unsuccessful.^{1, 6}

Moore and Murphy⁷ have recently reported an unusual case treated conservatively. After walled off had occurred, thoracotomy repair was successful. These authors suggest the use of the conservative measures of pleural drainage and jejunostomy, believing that, in many cases, the perforation will heal spontaneously. In the cases in which healing does not occur, operative intervention can be undertaken.

There are certain similarities in the development of this lesion to that of perforated peptic ulcer, and in a general way, one believes that correction of this defect should follow the same lines as the treatment of perforated peptic ulcer. It appears necessary that adequate drainage of the mediastinum, with closure of the perforation, be provided. Ideally, this is accomplished by thoracotomy, wide opening of the mediastinal pleura, closure of the esophageal defect, re-expansion of the lung and closure of the chest, with intercostal tube drainage. Attempts at such a procedure have been made by various surgeons. Collis⁸ and Foggett⁹ completed their operations successfully, but the patients died a few hours later. Kinsella's³ patient was well on the road to recovery, only to die of a pulmonary embolism on the ninth postoperative day. More recently, Barrett¹⁰ and Olsen and Claggett² have treated patients definitively with success.

The decision to undertake operation for such patients is not simple. These patients are acutely ill, their blood pressure is extremely low, and they are poor candidates for anesthesia. However, since the results without surgical repair are so disastrous, operation is justified despite the patient's condition at the time the patient is first seen. Obviously one first prepares the patient, as necessary, by thoracocentesis, gastric suction and transfusions. However, delay longer than a few hours will permit further deterioration of the patient's condition.⁶ One can be encouraged by the fact that immediately after opening of the mediastinal pleura, the patient should be considerably improved by relief of mechanical compression of mediastinal structures. In Case 2 reported below, the blood pressure remained at shock levels until the chest cavity was entered and the mediastinal pleura opened, the tension

within the mediastinum thus being relieved. From that time, the patient's blood pressure remained normal throughout the operation. This same sequence of events was also true in Barrett's¹⁰ successfully treated case.

CASE REPORTS

CASE 1 H M, a 45-year-old man, was admitted to the Mount Auburn Hospital on July 11, 1947, because of severe pain in the upper abdomen and lower chest. The patient had always been well until 3 months prior to admission, when he began to have dizzy spells, for which his physician was unable to find a cause. On the night of July 11, the patient felt nauseated and vomited. Because the feeling of nausea persisted, he attempted to make himself vomit. During one of these attempts, there was a sudden onset of severe pain in the left anterior portion of the chest and upper abdomen. The pain was unbearable from its onset, and a physician was called immediately. When seen, the patient was in shock, the temperature was subnormal, and the pulse 110. He was immediately sent to the hospital with a tentative diagnosis of coronary thrombosis.

At the time of admission, electrocardiogram and x-ray films of the abdomen were normal. A chest plate at that time (Fig. 1) showed a slight amount of fluid at the left base.

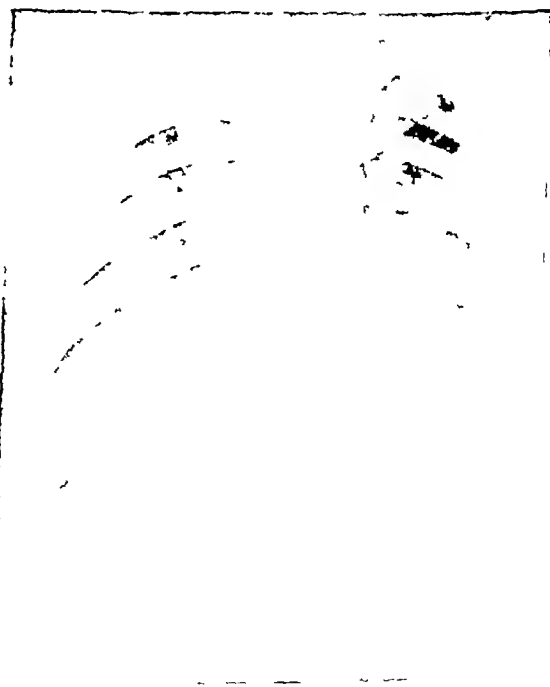


FIGURE 1 Posteroanterior Roentgenograms of the Chest on Admission in Case 1, Showing a Small Amount of Fluid at the Left Base

Twenty-four hours after admission, x-ray study revealed a pleural effusion filling the left side of the chest (Fig. 2). At that time the blood pressure was normal, the temperature was 100°F, and the pulse 110, and he was relatively comfortable. During the next 24 hours, the patient's condition deteriorated gradually, and a thoracic surgeon was consulted. Physical examination at that time showed that the trachea was deviated to the right. There was subcutaneous emphysema in the right supraclavicular fossa. The entire left side of the chest was flat to percussion, and the breath sounds were absent. The abdomen was voluntarily spastic, without tenderness or palpable masses.

A diagnosis of spontaneous perforation of the esophagus, with rupture of the mediastinal abscess into the pleural cavity, was made. Review of the previous x-ray films showed air present in the mediastinum (Fig 2)

Thoracentesis was performed immediately, and 500 cc. of seropurulent fluid was removed. Direct smear showed gram-positive cocci, culture of which later proved to be pneumococci. Because of the patient's poor condition and the fact that the lesion had been present for approximately 60 hours, radical operation was not considered. Intercostal drainage was accomplished, 1500 cc of purulent fluid being removed, after which the breath sounds were well heard throughout the left side of the chest. Penicillin and streptomycin were given in large doses. On the following day, the patient's condition was satisfactory, the tube was functioning well. There appeared to be atelectasis of the left lung, and endotracheal suction was performed, with immediate expansion of the lung. Constant gastric suction was instituted, and the patient was



FIGURE 2 *Posteroanterior Roentgenogram of the Chest Twenty-Four Hours after Admission in Case 1*

The left side of the chest is filled with fluid, and air can be seen in the upper mediastinum and neck

maintained on intravenous administration of fluids and transfusions

One week after admission, the patient's condition remained satisfactory, and a swallow of radio-opaque oil was given. This showed a definite perforation at the lower end of the esophagus, with the oil in the mediastinum and communicating with the pleural cavity.

On July 22 a rib-section drainage of the empyema was performed, and through the empyema cavity, a large mediastinal abscess was opened into the pleural cavity. Subsequently, the patient's condition appeared to become worse. There was considerable mobility of the underlying lung, and toxicity seemed to increase greatly. There was frequent regurgitation of gastric contents through the perforation into the empyema cavity. Such an incident usually coincided with a marked elevation of temperature. This was controlled by gastric suction. A jejunostomy was performed for feeding.

Four attempts to repair the linear laceration of the esophagus which was easily seen at the bottom of the empyema cavity, were made at intervals of 10 to 14 days, without success in spite of what appeared to be a completely adequate three-layer closure of the esophagus. The patient's condition gradually improved, and after these failures, no further attempts to close the esophagus were made. The patient was allowed up and about, and gradually, over a period of 1 month after the last attempt at closure, the laceration in the esophagus closed and he was able to take food by mouth.

He was discharged home on November 4, 1947, with a jejunostomy tube in place, the empyema cavity widely opened, and moderate amounts of food being taken by mouth. The patient's condition gradually improved at home. The empyema wound closed. The jejunostomy tube was withdrawn, and approximately 1 year after the original perforation, he was eating normally and was working full time. Operative closure of a persistent jejunostomy fistula was necessary 1½ years after the original episode.

Because the perforation had existed sixty hours before diagnosis, it did not appear that the patient's condition would allow a major surgical procedure at that time. Therefore, temporary drainage of the pleural cavity was performed with an intercostal tube, and, later, wide-open drainage of the mediastinal abscess and empyema accomplished. For approximately three months, this patient was extremely ill—at times, even moribund. Repeated transfusions were necessary, he presented a problem of hydration and nutrition at all times. He lost a considerable amount of weight during the first two months, despite jejunostomy. Eventually adequate feedings could be accomplished and the weight was regained.

Bacteriologically, the only organism cultured from the mediastinal abscess or pleural fluid was a pneumococcus. The fact that this was the only organism present may have contributed to his ability to withstand the infection.

Attempts to close the esophagus within the empyema cavity, despite adequate technical closure, were completely unsuccessful, since the suture line was bathed in the empyema pus and sloughing occurred within forty-eight hours of the time of repair. Yet the patient's condition was never such that one would consider decortication of the empyema, closure of the esophagus, re-expansion of the lung and closure of the chest wall. All these procedures would have been necessary to produce definitive operative closure after the first month. Awaiting natural closure provided a successful, if long delayed, cure.

CASE 2 J. R., a 56-year-old man, was admitted to St. Elizabeth's Hospital on April 26, 1948, because of pain in the epigastrium and lower chest. For 2 days prior to admission, he had vomited intermittently without other symptoms. At 4:30 a.m. on the day of admission, he was suddenly awakened by nausea and vomiting. He vomited for approximately ½ hour, retching severely with the vomiting. Suddenly, during an attack of vomiting, he was seized with severe, excruciating pain in the lower chest and upper abdomen. At that time, examination of the chest and abdomen by his physician was negative. The patient was in moderate shock, the pulse was rapid, and it was the examining physician's impression that the patient had a penetrating ulcer. Morphine was ordered, and the patient was told to remain at rest. A few hours later, because the pain persisted, he was hospitalized.

Physical examination showed the patient to be in severe shock and obviously toxic. There was slight cyanosis of the face and neck. There was marked venous distention of the neck and arms, with some crepitation in the right supraclavicular area. Examination of the chest was essentially negative except for diminished breath sounds at the left base. The abdomen showed slight tenderness and spasm.

X-ray examination of the chest and upper abdomen revealed air in the mediastinum (Fig. 3 and 4), and the diagnosis of spontaneous rupture of the esophagus was made.

Operation was performed approximately 30 hours after the onset of pain. Under endotracheal nitrous oxide, ox-

saline solution, and the lung re-expanded. One hundred thousand units of penicillin and 1 gm. of streptomycin were left in the pleural cavity. A No. 28 catheter was inserted through the tenth interspace for drainage. The chest wall was closed in layers, with interrupted catgut sutures and black silk to the skin.

The immediate postoperative course was uneventful. There was moderate drainage for 48 hours, after which the drainage tube ceased to function. The lung was well expanded immediately postoperatively and remained so. The temperature became normal on the 2nd postoperative day. The tube was left in place for 8 days because of a small posterior collection of fluid. Penicillin was continued for 8 days, and streptomycin for 4 days.

Administration of liquids was started on the 2nd postoperative day, and soft solids on the 5th day. On the 8th day, a small amount of methylene blue was given in water, and after 1 hour, the drainage within the intercostal tube showed a blue coloration. Because of this, open drainage of the posterior collection of fluid was performed. Two days later, a jejunostomy was performed, and the patient was fed through this for 10 days. From that time on there was no evidence of esophageal leakage. The patient was allowed to have a normal diet and was discharged home on June 5.



FIGURE 3 Posteroanterior Roentgenogram of the Chest on Admission in Case 2, Showing Air in the Mediastinum and Neck

There is a small pleural effusion on the left

xygen and ether anesthesia, the blood pressure was 70/40. The pulse was of good quality and rapid, and the respirations were shallow. In the right lateral decubitus position, a 25-cm. oblique incision was made over the ninth rib, and very slight bleeding was encountered. A 25-cm. segment of the rib was removed, and the pleura was opened. The pleura was grossly discolored, appearing edematous and alternately black and gray. There were thick, black fibrin clots over the pleural surface, and there was a moderate amount of thin, gray, dirty, odorless fluid within the pleural cavity. The lung, which was loosely adherent to the diaphragm, was freed. The mediastinal pleura was bulging, and when it was opened, there was a gush of dirty gray fluid and air from the mediastinum. The mediastinum was then widely opened, and the fluid removed. At this point, the blood pressure returned to normal and remained so thereafter. At the lower end of the esophagus, approximately 1 cm. above the diaphragm on the left anterolateral wall, was a 5-cm. vertical laceration, which involved the muscularis and mucosal coats, the edges, however, appeared entirely normal except for the reaction similar to that present throughout the mediastinum. There was no evidence of ulceration or tumor or stricture above or below the point of perforation. The mucosa was inverted with a running 000 catgut suture. The muscular layers were closed with interrupted catgut sutures. The pleural cavity was then irrigated with physiologic



FIGURE 4 Posteroanterior Film of the Upper Abdomen Taken in the Upright Position on Admission in Case 2, Showing the Air in the Mediastinum behind the Heart

The jejunostomy tube was left in place for 1 month as a safeguard and then removed. The wound closed spontaneously. The empyema pocket closed rapidly, being completely obliterated in 6 weeks.

Postoperative follow-up study during the next 6 months showed no evidence of complications. The patient was eating well. There was no pain in the chest, the lungs were normally expanded, and the diaphragm functioned normally.

This case served to emphasize a number of points. The first, and most important, was that the diagnosis was made by the roentgenologist from the roentgenogram of the abdomen and chest. Nevertheless, it was not immediately appreciated that surgical treatment was possible, since it was believed

that this was a fatal lesion. However, the time allowed to pass was of no importance in this case, but the outcome could have been more serious if too much time had elapsed.

Secondly, the case showed, strikingly, the effect of mediastinal compression on the blood pressure. Immediately after the mediastinum was opened and the fluid and gas were released, the pressure returned to normal. It has been suggested^{1, 3} that the early deaths are due to the mechanical compression of the vascular structures in the mediastinum, relief of which can be accomplished only by open drainage of the mediastinum. A reperforation at the site of repair apparently occurred in Case 2, but healing was rapid once rib-resection drainage of the empyema had been accomplished and jejunostomy feeding started. Generally, the results of operation, although not definitive, were most satisfactory and within a month of the onset, the patient was eating normally.

CASE 3. J. R., a 62-year-old man, was admitted to the Carney Hospital on November 12, 1948, with a history of severe chest pain of approximately 12 hours' duration. The patient stated that on the previous day he had consumed

time, he noted some sweating. His physician was called immediately.

Examination of the chest was negative. There was some tenderness with a slight spasm in the epigastrium. The blood pressure was 120/60, with a pulse of 100. The physician was unable to make a definite diagnosis and the patient was given morphine for pain. Re-examination on the following morning showed a further fall of the blood pressure, with an increase in the tenderness and spasm of the epigastrium. At this time, there was some dullness with diminished breath sounds at the left base, and because of this, the patient was hospitalized.

After admission, the course remained essentially unchanged. The patient preferred to sit up in bed and had a grunting-type of respiration, and there was increased spasm of the upper abdomen that appeared to be voluntary in type. There was slight subcutaneous emphysema in the right supraclavicular fossa.

The temperature was 103°F, the pulse 110, and the blood pressure 110/60.

X-ray examination, performed to rule out a perforated ulcer, showed air behind the heart (Fig. 5). A film of the



FIGURE 5. *Posteroanterior Roentgenogram of the Upper Abdomen Taken in the Upright Position on Admission in Case 3. This film clearly demonstrates the air behind the heart.*

a large amount of beer while eating a moderate amount of food. At approximately 10 p.m. he noted severe gastric distress. Because of this distress, he attempted to vomit, and after some time, he had moderate success. He continued his efforts to make himself vomit, and during a period of severe retching, he suddenly noticed a burning sensation in the center of his chest. Because this sensation was so painful, the patient had to sit upright and lean forward. At the same



FIGURE 6. *Posteroanterior Roentgenogram of the Chest on Admission, Showing Air in the Lower Mediastinum.*

chest taken at the same time showed widening of the mediastinum, with air in the mediastinum up to the neck (Fig. 6). The diagnosis of spontaneous perforation of the esophagus was made, and a thoracic surgeon was consulted. Immediate operation was advised and performed 12 hours after the onset.

Under endotracheal nitrous oxide, oxygen and ether anesthesia, the left side of the thorax was entered through the bed of the ninth rib. Cloudy, odorless fluid was found when the pleural cavity was entered. The lung was retracted, and the mediastinum was seen to be bulging. Immediately on opening of the mediastinal pleura, air escaped, and a large amount of dirty, gray fluid that had a faintly foul odor was obtained. A large piece of cabbage was found in the mediastinum. At the lower end of the esophagus at the left anterolateral wall a 3.8-cm laceration of a linear type was found. The mucosa pouted through the muscularis and appeared normal. The esophagus was mobilized at this

area, and the perforation closed with interrupted No 000 silk sutures. The mucosa was closed in a double layer. A flap of mediastinal pleura was developed and sutured down over the area of laceration. The mediastinum was opened widely up to the arch of the aorta. The pleural cavity was irrigated with physiologic saline solution, and 100,000 units of penicillin and 1 gm of streptomycin were left in the pleural cavity. A No 28 catheter was inserted through the tenth interspace for drainage. The lung was re-expanded, the chest wall was closed in layers with interrupted No 00 catgut sutures. The skin was closed with black silk.

The postoperative course was uneventful. Intramuscular administration of penicillin and streptomycin was continued postoperatively for 5 days. The intercostal tube drained satisfactorily for 48 hours and was removed after 72 hours in spite of a small amount of fluid that remained at the base posteriorly. The temperature remained normal from the 3rd day after operation. The patient was allowed out of bed on the 4th day. He was placed on a liquid diet from the 3rd day on, and was given a soft-solid diet on the 6th day. The patient was discharged on the 14th hospital day on a normal diet. The course thereafter remained satisfactory, and examination approximately 4 months after operation showed him to be in good physical condition. The lung was well expanded, he was taking a normal diet without difficulty.

This case represented the ideal of definitive treatment of this serious condition. Early diagnosis was possible because of early x-ray examination and the recognition of the significance of air in the mediastinum. Definitive operation was possible in spite of the patient's condition, and closure of the esophagus was adequate, allowing him to take a diet from the third day on. The possible presence of a foreign body in the mediastinum, such as previously ingested food, is demonstrated by this patient, and may further strengthen the indication for early surgical intervention.

DISCUSSION

Spontaneous perforation of the presumably normal esophagus may not be as rare as the number of reported cases indicates. Since early diagnosis gives the best chance of satisfactory treatment, it is stressed that there is usually a characteristic symptomatology. One should always suspect this condition in any case in which severe pain in the lower chest or upper abdomen occurs during vomiting. Although there are no early characteristic physical signs, the finding of subcutaneous air in the neck in a patient with this story is diagnostic. However, even in the earliest stage after onset,

x-ray study of the chest will show air or fluid behind the heart in the mediastinum. This, together with the characteristic story, should be diagnostic. A swallow of radio-opaque oil with fluoroscopic observation can be used if further proof of the diagnosis is desired.

Although one of the patients discussed above, as well as 3 in the literature, survived on a conservative routine of therapy, such an outcome should not be anticipated in most cases. The majority of the patients in the cases reported in the literature were treated conservatively, without survival. Early definitive operation aimed at closing of the perforation, relief of the mechanical compression of the mediastinum, expansion of the lung and drainage of the pleural cavity should prove to be more successful. With modern technics of anesthesia and thoracic surgery, aided by the antibiotics, operation generally provides the most satisfactory form of treatment for these seriously ill patients.

SUMMARY

The clinical picture of spontaneous perforation of the normal esophagus is briefly reviewed, and reference to more complete studies is made.

The case histories of 3 patients successfully treated surgically are presented and discussed.

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HYPERPARATHYROIDISM WITH NEPHROLITHIASIS*

Report of a Case with a Parathyroid Tumor Located Within the Thymus

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THE existence of severe hyperparathyroidism without bone disease has been well established since it was first demonstrated in 1937 by Albright, Sulkowitch and Bloomberg.¹ The chief clinical manifestation of hyperparathyroidism in these patients consists of kidney stones or nephrocalcinosis, or both, without roentgenographic abnormalities of the bone or increased amounts of alkaline phosphatase in the blood. In the large series of cases of hyperparathyroidism studied by Albright and his co-workers,^{1,2} kidney disease was more common than bone disease. The incidence of renal calculi was likewise high in the Mayo Clinic series reported by Keating and Cook;³ unilateral or bilateral renal calculi being present in 18 of 24 cases of hyperparathyroidism, renal calculi or calcification of the kidneys was present in 92 per cent of their series. A subsequent report from the Mayo Clinic by Black⁴ has emphasized the significant increase in the proved diagnosis of parathyroid adenoma when hyperparathyroidism is carefully and regularly sought in patients with renal lithiasis. Norris,⁵ however, in a study of 322 reported cases of hyperparathyroidism found bone involvement alone in 59 per cent and renal lithiasis or renal calcification without bone involvement in only 5 per cent. This is a striking discrepancy, which Norris himself ascribed to insufficient appreciation of the inter-relation between nephrolithiasis and hyperparathyroidism in many of the earlier cases. In any event, it is agreed that the commonest complication of hyperparathyroidism is precipitation of calcium salts in the urinary tract. This results from the associated hypercalcemia with the formation of calcium phosphate stones in alkaline urine or calcium oxalate stones in acid urine. Renal calcification or nephrocalcinosis results from the deposition of calcium casts in the kidney tubules or in the renal parenchyma.

The case reported below is noteworthy because it illustrates the frequently encountered difficulties in diagnosis when bone disease is absent, mild but prolonged hyperparathyroidism with striking recurrence of renal and ureteral calculi without bone involvement, an unusual location of a mediastinal

parathyroid tumor, and the treatment of severe urinary sepsis complicating the nephrolithiasis by antibiotic and chemotherapeutic agents selected in accordance with *in vitro* sensitivity tests of the pathogenic organisms.

CASE REPORT

F W. (B I H 98960), an 18-year-old girl, first entered the Beth Israel Hospital on April 21, 1947, complaining of severe, colicky pain in the right flank of 48 hours' duration. Chills, fever (temperature of 104°F), nausea and vomiting were present during the same period. She had had two similar attacks 5 and 9 months previously in both of which the symptoms had persisted for 48 hours. The past history was otherwise uneventful.

Physical examination revealed a well developed, acutely ill girl. The skin was hot and dry. The pupils were equal and reacted well to light and accommodation, and the extraocular reactions were normal. There were no abnormalities of the fundi. Examination of the ears, nose and throat revealed no abnormalities. There were no palpable masses, lymph nodes, thrills or abnormal pulsations in the neck. The thyroid gland was not enlarged. The breasts were normal. There were no palpable axillary or inguinal lymph nodes. The lungs were normal to palpation, percussion and auscultation. The heart was not enlarged; the sounds were forceful; the rhythm was regular, and there were no murmurs. The abdomen was soft and flat, with marked tenderness over the right costovertebral angle; no masses or organs were palpable. The extremities showed no edema. The knee jerks and ankle jerks were equal and active. The plantar reflexes were normal.

The temperature was 104°F, the pulse 150, and the respirations 30; the blood pressure was 120/70.

The urine was grossly bloody and contained numerous white cells. Culture of the bladder urine revealed *Pseudomonas aeruginosa*, *Aerobacter aerogenes* and *Bacterium calcaligeres*. The serum calcium was 11.0, 11.1 and 11.7 mg per 100 cc during the 8-day period from April 28 to May 6 (Table 1). Intravenous and retrograde pyelograms demonstrated a large, obstructing calculus in the pelvis of the right kidney and three small calculi in the lower calyx of the left kidney.

On the 4th hospital day a right pyelonephrolithotomy was done, with removal of the calculus. Chemical analysis of the stone showed it to consist of calcium phosphate.

Streptomycin in a dosage of 2 gm daily, penicillin in a dosage of 500,000 units daily and sulfadiazine in a dosage of 2 gm daily during the postoperative period had no effect on the pyuria or bacilluria. The patient was discharged on May 28, symptom-free and afebrile but with the urine still containing *Escherichia coli* and *A. aerogenes*. No attempt to remove the stones in the left kidney was made. The significance of the slight hypercalcemia was not appreciated at this time.

On June 21 the patient was readmitted because of left-flank pain, chills, fever (temperature of 104°F), malaise, nausea and vomiting. She was acutely ill and markedly dehydrated. There was tenderness over the left costovertebral angle. Urinalysis revealed pyuria and bacilluria. Culture of the urine showed *Esch. coli* and *A. aerogenes*. After 4 days' treatment with 2 gm of streptomycin daily and 2 gm of sulfadiazine daily the patient became afebrile and symptom free; the urine, however, remained infected with the same organisms. She was discharged on the 11th hospital day.

Five days after discharge the patient was again readmitted because of chills, fever, left-costovertebral-angle pain, nausea

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and vomiting. The temperature was 104.8°F, and the pulse 146. Retrograde pyelograms revealed two ureteral calculi in the region of the left ureterovesical junction and a larger stone in the left ureter at the level of the lower end of the sacrum. The lower ureteral calculi were removed by cystoscopic manipulation. Urine cultures at this time revealed *Esch coli*, *A. aerogenes* and *Ps. aeruginosa*. These organisms were resistant to streptomycin, penicillin, sulfadiazine and Mandelamine, both clinically and in vitro. The patient left

the hospital after 10 days, free of pain, but with an infected urine and a stone still present in the lower third of the left ureter. The bladder urine was sterile, but urine from the left nephrostomy showed *A. aerogenes*, *Esch coli* and *Ps. aeruginosa* on culture, although there was a marked decrease in the number of bacteria. The rapid formation of urinary calculi led to a search for hyperparathyroidism. Serum calcium determinations during the following 27 days showed values fluctuating between

TABLE 1 Pertinent Data on First Admission

DATE	NONPROTEIN NITROGEN mg /100 cc	TOTAL PROTEIN gm /100 cc	SERUM CALCIUM mg /100 cc	SERUM PHOSPHORUS mg /100 cc	ALKALINE PHOSPHATASE units /100 cc	IONIZED CALCIUM mg /100 cc
1947						
4/28	45	—	11.0	1.7	7.1	—
4/30	40	—	11.1	3.3	—	—
5/6	34	7.04	11.7	3.7	2.9	5.25

the hospital after 10 days, free of pain, but with an infected urine and a stone still present in the lower third of the left ureter.

She remained asymptomatic for 7 months, after which she again experienced an attack of left-flank pain associated with chills, fever (temperature of 103.6°F), nausea and vomiting. She was readmitted on February 25, 1948, acutely ill and markedly dehydrated. Excretory pyelograms disclosed

gradually returned to normal, with clinical improvement. The bladder urine was sterile, but urine from the left nephrostomy showed *A. aerogenes*, *Esch coli* and *Ps. aeruginosa* on culture, although there was a marked decrease in the number of bacteria.

The rapid formation of urinary calculi led to a search for hyperparathyroidism. Serum calcium determinations during the following 27 days showed values fluctuating between

TABLE 2 Pertinent Data on Fourth Admission

DATE	NONPROTEIN NITROGEN mg /100 cc	TOTAL PROTEIN gm /100 cc	SERUM CALCIUM mg /100 cc	SERUM PHOSPHORUS mg /100 cc	ALKALINE PHOSPHATASE units /100 cc	IONIZED CALCIUM mg /100 cc
1948						
2/27	40		12	1.7	3.9	
2/28	47	6.19	11.5	2.0		5.6
3/1			8.6	2.5	4.5	
3/3	40		9.1	3.0		
3/6	30		9.1	3.0		
3/7			8.6			
3/9			10.7	2.4		
3/11			10.6			
3/24			12.6			
3/25			12.7	3.5	3.3	
3/29			12.3	3.3		
4/3*			12.0	3.6		
4/6			11.3			
4/8			12.2	2.3		
4/15			11.7	2.8		
4/23			12.5			
5/11†			8.3	3.3	3.8	
5/12			8.2			
5/13	44	6.56	8.9	3.8	5.4	4.1
5/14		7.52	9.6	3.1		4.1
5/17		7.30	8.9	3.6	3.9	3.8
5/18			9.2	3.9		
5/19			9.1	3.6		
5/20	36		10.4	4.3		4.0
5/24		7.70	9.6	4.4	3.2	3.4
5/26		8.00	8.5	4.0	2.9	3.7
5/28		8.47	9.6	4.0	3.6	
6/17			9.9	3.6		
6/24			9.7			
6/29			10.0	3.8		
7/7			9.8	4.0		
7/14			9.7	3.1	2.1	
7/27	31		9.8	3.8		
8/3	34		9.7	4.2		
8/19	27					

*Cervical exploration performed on preceding day.

†Mediastinal operation (removal of parathyroid tumor) performed on preceding day.

a large obstructing calculus in the left renal pelvis and multiple smaller calculi in the lower calyx. A ureteral catheter could not be passed by the stone in the renal pelvis. The clinical course was characterized by recurrent chills and persistent fever, the temperature often reaching 105°F. A left pyelonephrolithotomy and nephrostomy were done on the morning after admission. The kidney was edematous, and its surface studded with small abscesses. The large stone in the pelvis was easily located and removed. The smaller calculi in the lower calyx were not removed because the pa-

12.7 and 8.6 mg per 100 cc (Table 2). The serum inorganic phosphorus levels ranged from 3.6 to 1.7 mg per 100 cc (Table 2). The Sulkowitch test, performed on urine obtained at 8-hour intervals each day for 14 days, varied from ++ to ++++ while the patient was on a low-calcium diet (0.22 gm of calcium per 2000 calories). Roentgenodiet (0.22 gm of calcium per 2000 calories) showed no decalcification or cyst formation. The calculus removed from the

*Dr. Fritz H. Schweinburg generously co-operated in the performance of the bacteriologic and in vitro sensitivity studies.

kidney was examined by Dr E L Prien, utilizing the method of optical crystallography, and found to consist of 95 per cent calcium phosphate⁶

In view of the recurrent nephrolithiasis, hypercalcemia and hypophosphatemia and the nature of the removed stone a diagnosis of hyperparathyroidism was made, and parathyroidectomy undertaken

The first operation consisted of a cervical exploration by Dr J Fine on April 2, 1948. Both thyroid lobes were fully exposed and examined without disclosure of any abnormalities. Exploration posterior to the trachea and esophagus and of all cervical tissues up to the hyoid bone and down to the jugular notch revealed no evidence of parathyroid tumor.

After this operation the abnormal values of serum calcium and inorganic phosphorus persisted (Table 2). The urinary infection was treated in succession with 5 gm of Mandelamine, 6 gm of sulfamethazine, 2 gm of sulfathiazole and 6 gm of sulfathaladine daily, with some clinical and bacteriologic improvement but without rendering the urine sterile. A second operation for the relief of the hyperparathyroidism was therefore undertaken on May 10 by Dr Fine. The anterior mediastinum was explored through a sternum-splitting incision. No parathyroid tumor was found in the plane anterior to the thymus. Accordingly, the thymus itself was dissected free from the underlying great veins. The lower pole of the left lobe was enlarged and on palpation contained a firm, discrete nodule about 5 mm in diameter buried in its substance. The thymus with its contained nodule was therefore removed. Examination of the nodule by frozen section showed it to consist of parathyroid tissue. Further exploration of the anterior mediastinum from the thoracic

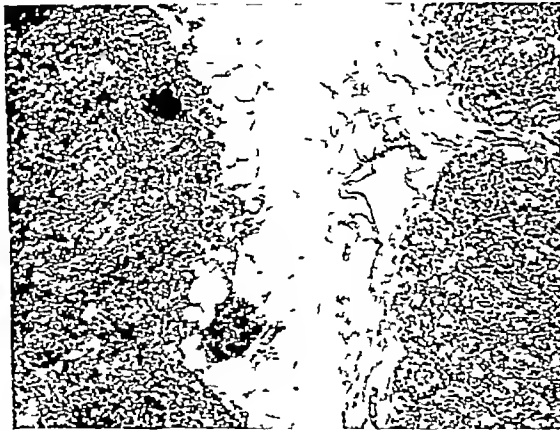


FIGURE 1 Section Showing the Thymus at the Left and the Parathyroid Nodule at the Right. Note the acinar and tubular arrangement of the parathyroid cells and basal orientation of the nuclei ($\times 100$)

inlet to the top of the pericardium, anterior and posterior to the innominate veins and superior cava, disclosed no further evidence of parathyroid tissue.

On pathological examination the thymus was roughly triangular in shape and measured 3.5 cm in width, 3.5 cm in length and 0.4 cm. in thickness, and had the appearance of fibrofatty tissue. Near one of the angles a small nodular mass with the consistency of a lymph node was palpated. When dissected it had the shape and size of a small bean, measuring 4.5 by 4.0 by 5.5 mm. This was the same parathyroid nodule examined by frozen section at operation. Microscopical examination of the nodule showed a thin, incomplete fibrous-tissue capsule. No fat cells were enclosed in the section. The nodule was fairly vascular throughout. The epithelial cells comprising the nodule were present in bands and nests. There was a rich reticular and capillary

network, free of congestion. The bulk of the epithelial cells were very similar in appearance. In the smaller nests the peripheral cells in contact with the reticular stroma tended to become polarized. Occasionally, the polarized cells surrounded a lumen measuring 12 to 20 microns in diameter and containing in some areas deeply eosinophilic staining non-granular material. In many nests, particularly the larger ones, there was no tendency to polarization. The epithelial cells generally showed a thin but distinct cell wall, which was most obvious in the polarized cells. Their cytoplasm was quite uniform in appearance, finely granular, pale and acidophilic. The nuclei of the epithelial cells were round to oval and showed a fairly uniform size, measuring 10 to 15 microns. There was abundant chromatin arranged in a uniform, coarsely granular pattern in a nongranular, fainter basophilic background. About 10 per cent of the nuclei had

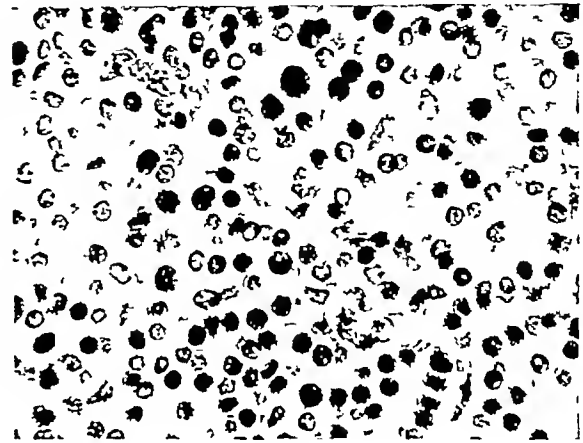


FIGURE 2 Section of Parathyroid "Tumor," Showing Moderate Variation in Cell Size and Density of Staining of the Nuclei ($\times 500$)

one or more nucleoli. No mitoses were seen. In occasional small areas the epithelial cells were larger with a paler, looser cytoplasm. The nuclei of these cells were larger and paler with more prominent nucleoli. These cells showed little polarization. They resembled but were not typical "wasserhelle" cells. Scattered through the sections were individual small clumps of "oxyphil" cells, which were more rounded and larger than the majority of the epithelial cells of the nodule. These cells had a more eosinophilic and slightly granular cytoplasm, with dark, round pyknotic nuclei (Fig 1 and 2).

After operation the patient received a high-calcium diet with dihydrotachysterol (A.T. 10) for 5 days to prevent tetany. The serum calcium on the 1st postoperative day was 8.3 mg per 100 cc of blood, and the serum inorganic phosphorus 3.3 mg per 100 cc of blood (Table 2). Serum calcium values during the subsequent 3-week period varied between 8.2 mg and 9.6 mg, and the serum phosphorus ranged between 3.3 and 3.8 mg per 100 cc. Clinically, the immediate postoperative course was uneventful, although the urine still remained infected.

As a result of the recurrent nephrolithiasis, surgical manipulation and persistent urinary infection, a complete stricture developed at the left ureteropelvic junction. Repeated dilatations over a 3-month period were unsuccessful in overcoming the obstruction. The patient continued to have attacks of chills and fever, although no new calculi were observed. Cultures of the urine from the right kidney and bladder showed many colonies of *Ps. aeruginosa* and *A. aerogenes*, whereas the cultures from the left nephrostomy tube showed *Ps. aeruginosa*, *Esch. coli*, *A. aerogenes*, *Streptococcus faecalis* and paracolon bacilli. These organisms were resistant to sulfanilamide, sulfathiazole, sulfadiazine, sulfamethazine, NU 445, penicillin and streptomycin in vitro.

However, all strains except *Ps aeruginosa* were very sensitive to aureomycin*.

Aureomycin in a dosage of 10 mg was given intramuscularly twice daily for 10 days without reaction except for pain at the site of injection. Twenty-four hours after the initiation of therapy with aureomycin, urine from the right kidney and bladder was found sterile by culture (Fig 3). Urine from the nephrostomy tube still produced a heavy growth of *Ps aeruginosa*. Irrigations of the left renal pelvis with

then 10 mg twice daily for the next 4 days, streptomycin in a dosage of 2.0 gm was also given daily. Urine from the right kidney and bladder became sterile in 24 hours and remained so throughout the hospital stay. The postoperative course was uneventful, the temperature returning to normal in 3 days. Four weeks postoperatively the patient was asymptomatic and free of urinary infection, as shown by a clear urine, which was free of abnormalities of the sediment or bacterial growth (Fig 4).

The patient was seen in the Out-Patient Department 4 months after removal of the parathyroid tumor. She was asymptomatic, and physical examination showed no abnormalities. The serum calcium was 8.2 mg, serum phosphorus 3.2 mg, total protein 6.8 gm, and ionized calcium 3.5 mg per 100 cc. The urine was sterile on culture and contained no abnormalities of the sediment. By January, 1949 (3 months after parathyroidectomy), she had gained 22 pounds in weight. A roentgenogram of the genitourinary tract at this time revealed no calculi. The urine was sterile on culture. The serum calcium measured 9.9 mg, serum phosphorus 3.4 mg, and total protein 6.7 gm per 100 cc, with an ionized calcium of 4.7 mg. The serum calcium 10 months after parathyroidectomy was 9.5 mg per 100 cc.

In this case of hyperparathyroidism, recurrent renal and ureteral calculi were complicated by severe bilateral urinary-tract infection. On the first admission a large obstructing calculus in the pelvis of the right kidney and three small calculi in the lower calyx of the left kidney were demonstrated, in association with marked pyuria and bacilluria. Serum calcium and phosphorus determinations revealed mild hypercalcemia and hypophosphatemia. The stone in the right kidney was removed surgically, but the stones in the left kidney were untouched. Streptomycin, penicillin and sulfadiazine had no effect on the urinary-tract infection. Two months after the first admission the patient was readmitted because of recurrent urinary sepsis. On this admission two ureteral calculi were removed from the lower end of the left ureter by cystoscopic manipulation. The organisms present in the urine were resistant to streptomycin, penicillin, sulfadiazine and Mandelamine both clinically and in vitro. The patient was discharged with an infected urine and a left ureteral stone. Seven months later she was readmitted with recurrent symptoms of urinary infection. A large obstructing calculus in the pelvis of the left kidney was surgically removed, but multiple smaller calculi in the lower calyx of the kidney were left. Optical crystallography of the removed calculus showed it to consist of calcium phosphate. Urine culture still revealed a marked pyuria and bacilluria. In vitro sensitivity tests showed NU 445 and sulfathiazole to be bactericidal to these organisms. These drugs temporarily cleared the urinary infection of the right kidney, but urine from the left nephrostomy continued to show a heavy growth of bacteria. At this point a clinical diagnosis of hyperparathyroidism was established by the finding of hypercalcemia and hypophosphatemia and hypercalcuria. A hyperfunctioning parathyroid tumor was discovered, after a negative exploration of the neck, in the substance of the thymus gland

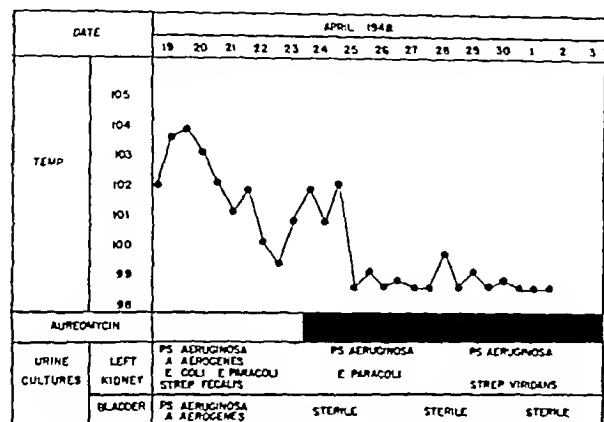


FIGURE 3 Effect of Aureomycin before Nephrectomy

aureomycin (1 mg in 10 cc of physiologic saline solution) through the nephrostomy were not bactericidal. After termination of therapy, urine from the right kidney and bladder continued to be sterile. Urine from the left kidney, however, showed a moderate growth of *Ps aeruginosa*.

Two weeks later the patient again experienced pain in the left flank associated with chills, fever (temperature of 103°F), nausea and vomiting. The infection again involved both

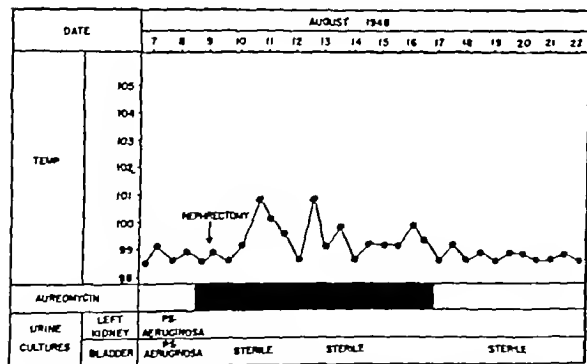


FIGURE 4 Effect of Aureomycin after Nephrectomy

kidneys and bladder, and there were positive cultures of *Ps aeruginosa* and *Esch coli* in the urine.

Because of the persistent urinary-tract infection and the multiple calculi in the lower calyx of the left kidney, an attempt was made to correct the obstruction at the uretero-pelvic junction. At operation the severe inflammatory reaction, dense adhesions and an intrarenal location of the pelvis rendered plastic procedures impossible so that a nephrectomy was performed.

After nephrectomy, the patient received 20 mg of aureomycin intramuscularly twice daily for the first 3 days, and

*This antibiotic was supplied by the Lederle Laboratories Division of the American Cyanamid Company, New York City.

†The strain of *Ps aeruginosa* isolated from the bladder was resistant in vitro to streptomycin.

The serum calcium returned to normal on the first postoperative day and subsequently remained normal.

During all hospital admissions the urinary infection proved resistant *in vitro* and clinically to penicillin, streptomycin, sulfadiazine, sulfamethazine and Mandelamine NU 445 and sulfathiazole had a transitory beneficial effect. Aureomycin⁹ quickly cleared the infection of the right kidney and bladder (Fig 3). However, the left kidney, because of an impassable stricture at the ureteropelvic junction and the presence of calculi remained infected and caused severe clinical symptoms until removed.

DISCUSSION

Although the number of reported cases of hyperfunctioning parathyroid adenoma now numbers almost 400 and the essential features of the syndrome have been well described, the present case illustrates the difficulties of achieving diagnosis and cure when the tumor is small, obscurely located and associated with minimal hyperfunction.

Albright and Reifenstein² have pointed out that hyperparathyroidism may exist in 4 clinical forms, tabularly represented as follows:

	BONE DISEASE	KIDNEY DISEASE
(A)	Present	Absent
(B)	Present	Present
(C)	Absent	Present
(D)	Absent	Absent

Hyperparathyroidism without bone or kidney disease has been reported but once, in this form diagnosis must initially depend upon characteristic blood chemical findings and clinically could only be suspected from the symptom of polyuria. The other forms of hyperparathyroidism are common and offer diagnostic clues either in the presence of bone disease such as osteitis fibrosa cystica or kidney disease as nephrolithiasis or, more rarely, as renal calcification.

The starting point in the diagnosis of hyperparathyroidism is a problem in quantitative chemistry. One must know the precise range of normal values for the method utilized in the hospital laboratory. If the total protein level is normal, serum calcium values above 11 mg per 100 cc must be regarded as suspect when associated with nephrolithiasis, osteoporosis, osteitis fibrosa cystica or unexplained polyuria. If there is simultaneous depression of the serum phosphorus level the diagnosis becomes increasingly certain.

It is clear that there is little diagnostic problem in cases in which the serum calcium is above 12 mg with characteristic bone changes. Difficulties arise, however, in cases like the present, in which bone changes were completely absent and the serum calcium persistently hovered about 11 mg per 100 cc, occasionally dropping to completely normal values (Table 2) or occasionally rising to slightly

abnormal values. In these situations the use of the Sulkowitch test as an index of calcuria is important, since the demonstration of a high-calcium output in the urine, with normal or slightly elevated serum calcium, should lead to further search for hyperparathyroidism. Several factors influence the interpretation of the Sulkowitch test, especially the previous diet, the concentration of the urine, the age of the patient and the presence or absence of renal disease. For this reason serial tests are most informative, the simplicity of the test lending itself readily to this purpose.

The degree of elevation of the serum calcium and consequently the degree of depression of the serum phosphorus is roughly proportional to the size of the tumor¹⁰ except in larger adenomas, when the proportionality is less. The smallness of the tumor in the present case was entirely consistent with the minimal elevations of the serum calcium observed at the first and fourth admissions. The tumor size, however, does not explain the sudden decline of the calcium values to normal or subnormal values during the fourth admission (Table 2) for a period of six days, followed by a return to slight hypercalcemia. An increased phosphate intake in the diet could explain such a decrease but would be accompanied by an elevation of the serum phosphorus level. Since this did not occur the explanation is more likely to be found in the intravenous infusion of saline solutions, which were given during this period because of the patient's condition. Physiologic saline solution, according to Albright and Reifenstein,² is a useful agent in parathyroid poisoning, presumably through a temporary effect in lowering the blood calcium.

Although small tumors do not elevate the blood calcium very much, this minimal elevation is entirely adequate for the production of nephrolithiasis in the severe form exhibited by this patient with both multiple stones, a rapid rate of stone formation and severely damaging renal infection.

Whereas the reported figures of parathyroid adenomas that are completely mediastinal have varied from 7 to 17 per cent,^{4, 5, 11} the number that are completely intrathymic is extremely small. Cope¹¹ has reported only 3 such tumors in his large series, whereas Norris,⁵ in his collective review of 322 cases, mentions 9. Embryologically, the intrathymic location is readily explicable because the lower parathyroid glands develop in close proximity to the thymus gland, descending partially with it but usually dropping off opposite the lower pole of the thyroid gland. Occasionally, however, the parathyroid glands grow down into the mediastinum adjacent to or within the body of the thymus gland.

The nature of the parathyroid lesion in this case was clearly that of a hyperfunctioning tumor or adenoma, since removal of a single, encapsulated nodule resulted in rapid and permanent disappearance of the signs and symptoms of hyperpara-

thyroidism Hyperparathyroidism resulting from primary hyperplasia always involves all four parathyroid glands and therefore will not remit with removal of a single gland

The early diagnosis of hyperparathyroidism is particularly important because the nephrolithiasis or nephrocalcinosis frequently associated with the disease may lead to irreparable kidney damage or prolonged renal infection with loss of a kidney, as illustrated by the case reported above Chemotherapy based on in vitro sensitivity tests, combined with relief of obstruction and removal of an infected kidney, led to eventual clearing of the sepsis of the genitourinary tract

SUMMARY

A case of hyperparathyroidism with nephrolithiasis and without bone disease caused by a small intrathyroidic parathyroid tumor is reported Complete clinical cure of the hyperparathyroidism followed removal of the parathyroid lesion

The difficulties in the clinical diagnosis are discussed

Genitourinary sepsis of severe degree was the chief complication This sepsis was eventually con-

trolled by nephrectomy and the selection of appropriate antibiotics on the basis of in vitro sensitivity tests

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CONDITIONED-REFLEX TREATMENT OF ALCOHOLISM

II. The Risks of Its Application, Its Indications, Contraindications and Psychotherapeutic Aspects

JOSEPH THIMANN, M.D.*

BOSTON

IN THE first article about the conditioned-reflex therapy its rationale and technic were discussed¹ The purpose of the present study is to show the risks, indications, contraindications, efficacy and psychotherapeutic aspects

To establish a reflex association between alcoholic beverages and vomiting, emetine hydrochloride is used as the unconditioned stimulus The pharmacologic interest in emetine started with its use for treatment of amebic dysentery, liver abscesses and alveolar pyorrhea

Emetine is one of the alkaloids of ipecacuanha Its pharmacologic properties were the object of extensive studies during the greater part of the nineteenth century However, not until 1893 did Paul and Cownley² demonstrate that the so-called emetine of previous workers was in reality a mixture of two alkaloids, emetine and another one, which they called "cephaeline"

Two years later, the pure emetine was for the first time investigated by Wild,³ who studied its emetic and other properties He found that it lowered the blood pressure and in excessive doses caused an arrest of the heart in diastole

The mode of excretion of emetine could not be determined No traces were found in gastric or intestinal contents or in the urine Baermann and Heinemann⁴ have stated that "with moderate sized doses of 60 to 150 mg there are no symptoms"

If 120 to 150 mg are given in daily repeated injections, there appear, after three or four injections, malaise, lassitude, slight vertigo and loss of appetite These symptoms disappear in from 24 to 72 hours after the emetine has been discontinued

Vedder⁵ called attention to the fact that rabbits died after small intravenous doses of emetine and advised strongly against the intravenous application in human beings

Other investigators described the gastrointestinal side effects such as nausea, vomiting and diarrhea

Levy and Rowntree⁶ cited several observers with 20 case histories One of these patients received a total dosage of 1.45 gm (24 gr.), another 1.28 gm (21 gr.), and a third 1.75 gm (29 gr.) The first 2 patients recovered although not without a transitory phase of diarrhea and a mild peripheral neuritis

A recent paper by Dack and Moloshok⁷ cited Heilig and Visveswar, who "failed to observe any significant alteration in the EKG, blood pressure

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or orthodiagram of 14 patients treated with twelve intramuscular injections of 1 grain (0.06 gm) of emetine hydrochloride daily." Hardgrove and Smith, cited in the same paper, observed in a series of 72 patients only 1 serious cardiac effect. They concluded that emetine hydrochloride in therapeutic doses produced only minor and transient electrocardiographic changes and that there was little risk involved in the use of emetine hydrochloride if electrocardiograms were taken during the course of treatment and the patient was kept in bed.

Dack and Moloshok discussed further their own observations of 9 patients, who were treated for amebic dysentery with emetine hydrochloride. The total dose ranged from 0.45 to 1.42 gm (7 to 22 gr). The neuromuscular manifestations of toxicity such as general muscular aching and weakness, tremor of the hands and dizziness usually appeared during the period of administration of emetine hydrochloride. In 8 of these cases, however, an abnormal electrocardiogram was not demonstrated until two to twenty-one days after the last injection of emetine.

The clinical examination of the cardiovascular system in these 9 cases did not show strikingly abnormal findings. Three patients displayed moderate tachycardia at rest and after mild effort. In 1 patient it was associated with presystolic gallop rhythm. Another patient complained of a mild precordial discomfort. In 5 cases there was dyspnea and fatigue of various degrees on exertion. None of the patients showed any abnormality in the size or configuration of the heart by x-ray examination. There was no significant lowering of the blood pressure.

In 3 cases diarrhea occurred during the course of treatment. The symptoms disappeared spontaneously when the use of emetine was discontinued.

The authors recommend absolute rest in bed during the course of treatment, daily recordings of the pulse rate at frequent intervals (tachycardia may be the first clinical sign of toxic effect), the patient should be examined and questioned at least daily for diarrhea, fatigue, dyspnea on exertion, muscular tremors or weakness and dizziness, an electrocardiogram should be taken before the treatment is instituted, after the fifth grain, at the completion of the course of the treatment and one week later (use of the drug should be discontinued if significant changes are found), emetine should not be used in the presence of organic heart disease and should be used with great caution in patients who are anemic and debilitated.

It may be recalled that the first report about the use of emetine for treatment of alcohol addiction was presented by Voegtlin⁸ in 1940.

Less than two years later the conditioned-reflex therapy by means of emetine was started for the first time on the eastern seaboard at the Wash-

ingtonian Hospital in Boston, 282 patients have been treated to date.* Their ages ranged from seventeen to sixty-four years. The total dose of emetine hydrochloride, as injected subcutaneously, during the initial series of six to seven daily sessions, varied from 0.5 gm (7.5 gr) to 0.85 gm (13¼ gr). Lately, it has been found that a series consisting of six sessions suffices to establish the reflex. This reduced the total dose to 0.675 gm (11¼ gr). As mentioned in the previous article¹ the patient receives prior to the injection a capsule containing 60 to 150 mg (1 to 2½ gr) of additional emetine hydrochloride by mouth with 1 to 3 glasses of water. It is assumed that very little of this additional emetine is absorbed because, after the dissolution of the capsule, the emetine becomes dissolved or suspended in the water contained in the stomach, most of which is vomited as soon as the emesis begins.

All but a few of the 282 patients treated reacted after two to four injections with diarrhea, mostly of a mild degree (two to five bowel movements daily). Only nine patients (3.19 per cent) claimed ten to fifteen bowel movements daily. Discontinuance of emetine injections for one to several days, combined with generous doses of kapectate, stopped the diarrhea. The initial series was continued, if necessary, with additional intermissions. Ten patients complained of cramping pain of the intestines or genitals, but only during the treatment sessions, when the emetine (and pilocarpine?) action was at its peak. The end of the treatment session, sometimes with the aid of a hot-water bottle, terminated the spasms.

Other side effects of emetine application were the neuromuscular disturbances. Ten to fourteen days after the initial series approximately 60 per cent of all patients treated displayed general muscular weakness and aching, especially in the lower extremities. The degree of these neuromuscular manifestations was light to moderate. The patients were able to walk and to climb and descend stairs without too much inconvenience. In only 2 cases (0.7 per cent) — both female patients, incidentally — the degree of the neuromuscular involvement was such that the patients were, for two or three weeks, able to walk on level ground only. All these neuromuscular manifestations, however, were safely overcome, at the latest, after several weeks of convalescence. Thus, all the side effects described above were mild.

Only 5 patients out of 282 treated with emetine (1.43 per cent) reacted with cardiovascular manifestations of any degree of severity.

One of these patients was a thirty-year-old, husky man. His electrocardiogram was described by the cardiologist as indicating a moderate degree of myocardial fibrosis — not extensive enough to

*This figure includes female patients who had to be treated outside the Washingtonian Hospital because of the lack of facilities for such patients.

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or orthodiagram of 14 patients treated with twelve intramuscular injections of 1 grain (0.06 gm) of emetine hydrochloride daily." Hardgrove and Smith, cited in the same paper, observed in a series of 72 patients only 1 serious cardiac effect. They concluded that emetine hydrochloride in therapeutic doses produced only minor and transient electrocardiographic changes and that there was little risk involved in the use of emetine hydrochloride if electrocardiograms were taken during the course of treatment and the patient was kept in bed.

Dack and Moloshok discussed further their own observations of 9 patients, who were treated for amebic dysentery with emetine hydrochloride. The total dose ranged from 0.45 to 1.42 gm (7 to 22 gr). The neuromuscular manifestations of toxicity such as general muscular aching and weakness, tremor of the hands and dizziness usually appeared during the period of administration of emetine hydrochloride. In 8 of these cases, however, an abnormal electrocardiogram was not demonstrated until two to twenty-one days after the last injection of emetine.

The clinical examination of the cardiovascular system in these 9 cases did not show strikingly abnormal findings. Three patients displayed moderate tachycardia at rest and after mild effort. In 1 patient it was associated with presystolic gallop rhythm. Another patient complained of a mild precordial discomfort. In 5 cases there was dyspnea and fatigue of various degrees on exertion. None of the patients showed any abnormality in the size or configuration of the heart by x-ray examination. There was no significant lowering of the blood pressure.

In 3 cases diarrhea occurred during the course of treatment. The symptoms disappeared spontaneously when the use of emetine was discontinued.

The authors recommend absolute rest in bed during the course of treatment, daily recordings of the pulse rate at frequent intervals (tachycardia may be the first clinical sign of toxic effect), the patient should be examined and questioned at least daily for diarrhea, fatigue, dyspnea on exertion, muscular tremors or weakness and dizziness, an electrocardiogram should be taken before the treatment is instituted, after the fifth grain, at the completion of the course of the treatment and one week later (use of the drug should be discontinued if significant changes are found), emetine should not be used in the presence of organic heart disease and should be used with great caution in patients who are anemic and debilitated.

It may be recalled that the first report about the use of emetine for treatment of alcohol addiction was presented by Voegtlin³ in 1940.

Less than two years later the conditioned-reflex therapy by means of emetine was started for the first time on the eastern seaboard at the Wash-

ingtonian Hospital in Boston, 282 patients have been treated to date.* Their ages ranged from seventeen to sixty-four years. The total dose of emetine hydrochloride, as injected subcutaneously, during the initial series of six to seven daily sessions varied from 0.5 gm (7.5 gr) to 0.85 gm (13¼ gr). Lately, it has been found that a series consisting of six sessions suffices to establish the reflex. This reduced the total dose to 0.675 gm (11¼ gr). As mentioned in the previous article¹ the patient receives prior to the injection a capsule containing 60 to 150 mg (1 to 2½ gr) of additional emetine hydrochloride by mouth with 1 to 3 glasses of water. It is assumed that very little of this additional emetine is absorbed because, after the dissolution of the capsule, the emetine becomes dissolved or suspended in the water contained in the stomach, most of which is vomited as soon as the emesis begins.

All but a few of the 282 patients treated reacted after two to four injections with diarrhea, mostly of a mild degree (two to five bowel movements daily). Only nine patients (3.19 per cent) claimed ten to fifteen bowel movements daily. Discontinuance of emetine injections for one to several days, combined with generous doses of kapectate, stopped the diarrhea. The initial series was continued, if necessary, with additional intermissions. Ten patients complained of cramping pain of the intestines or genitals, but only during the treatment sessions, when the emetine (and pilocarpine?) action was at its peak. The end of the treatment session, sometimes with the aid of a hot-water bottle, terminated the spasms.

Other side effects of emetine application were the neuromuscular disturbances. Ten to fourteen days after the initial series approximately 60 per cent of all patients treated displayed general muscular weakness and aching, especially in the lower extremities. The degree of these neuromuscular manifestations was light to moderate. The patients were able to walk and to climb and descend stairs without too much inconvenience. In only 2 cases (0.7 per cent) — both female patients, incidentally — the degree of the neuromuscular involvement was such that the patients were, for two or three weeks, able to walk on level ground only. All these neuromuscular manifestations, however, were safely overcome, at the latest, after several weeks of convalescence. Thus, all the side effects described above were mild.

Only 5 patients out of 282 treated with emetine (1.43 per cent) reacted with cardiovascular manifestations of any degree of severity.

One of these patients was a thirty-year-old, husky man. His electrocardiogram was described by the cardiologist as indicating a moderate degree of myocardial fibrosis — not extensive enough to

*This figure includes female patients who had to be treated outside the Washington Hospital because of the lack of facilities for such patients.

thyroidism Hyperparathyroidism resulting from primary hyperplasia always involves all four parathyroid glands and therefore will not remit with removal of a single gland

The early diagnosis of hyperparathyroidism is particularly important because the nephrolithiasis or nephrocalcinosis frequently associated with the disease may lead to irreparable kidney damage or prolonged renal infection with loss of a kidney, as illustrated by the case reported above Chemotherapy based on in vitro sensitivity tests, combined with relief of obstruction and removal of an infected kidney, led to eventual clearing of the sepsis of the genitourinary tract

SUMMARY

A case of hyperparathyroidism with nephrolithiasis and without bone disease caused by a small intrathymic parathyroid tumor is reported Complete clinical cure of the hyperparathyroidism following removal of the parathyroid lesion

The difficulties in the clinical diagnosis are discussed

Genitourinary sepsis of severe degree was the chief complication This sepsis was eventually con-

trolled by nephrectomy and the selection of appropriate antibiotics on the basis of in vitro sensitivity tests

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CONDITIONED-REFLEX TREATMENT OF ALCOHOLISM

II. The Risks of Its Application, Its Indications, Contraindications and Psychotherapeutic Aspects

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IN THE first article about the conditioned-reflex therapy its rationale and technic were discussed¹ The purpose of the present study is to show the risks, indications, contraindications, efficacy and psychotherapeutic aspects

To establish a reflex association between alcoholic beverages and vomiting, emetine hydrochloride is used as the unconditioned stimulus The pharmacologic interest in emetine started with its use for treatment of amebic dysentery, liver abscesses and alveolar pyorrhea

Emetine is one of the alkaloids of ipecacuanha Its pharmacologic properties were the object of extensive studies during the greater part of the nineteenth century However, not until 1893 did Paul and Cownley² demonstrate that the so-called emetine of previous workers was in reality a mixture of two alkaloids, emetine and another one, which they called "cephaeline"

Two years later, the pure emetine was for the first time investigated by Wild,³ who studied its emetic and other properties He found that it lowered the blood pressure and in excessive doses caused an arrest of the heart in diastole

The mode of excretion of emetine could not be determined No traces were found in gastric or intestinal contents or in the urine Baermann and Heinemann⁴ have stated that "with moderate sized doses of 60 to 150 mg there are no symptoms"

If 120 to 150 mg are given in daily repeated injections, there appear, after three or four injections, malaise, lassitude, slight vertigo and loss of appetite These symptoms disappear in from 24 to 72 hours after the emetine has been discontinued

Vedder⁵ called attention to the fact that rabbits died after small intravenous doses of emetine and advised strongly against the intravenous application in human beings

Other investigators described the gastrointestinal side effects such as nausea, vomiting and diarrhea

Levy and Rowntree⁶ cited several observers with 20 case histories One of these patients received a total dosage of 1 45 gm (24 gr), another 1 28 gm (21 gr), and a third 1 75 gm (29 gr) The first 2 patients recovered although not without a transitory phase of diarrhea and a mild peripheral neuritis

A recent paper by Dack and Moloshok⁷ cited Heilig and Visveswar, who "failed to observe any significant alteration in the EKG, blood pressure

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individual psychotherapy After several failures to prevent relapses, his therapist referred him for conditioned-reflex therapy When the patient completed his initial series of the conditioned-reflex therapy, he was advised to return four weeks later for his first reinforcement Circumstances delayed his return by an additional three months As it happened he was able to abstain from drinking for those four months, but when he again, for external reasons, postponed his second reinforcement he relapsed He then accepted the suggestion of a full retreatment, and six years later was able to report that he was apparently completely cured

Intrinsic reasons for relapse observed in these patients include an ambivalent attitude regarding abstinence, poor rapport with the therapist (father hostility) and subsequent rejection of follow-up psychotherapy and neurotic difficulties in facing life without the crutch — alcohol Such recidivists have naturally a poor prognosis

The indications for the conditioned-reflex therapy may be conceived in a twofold way From a narrow point of view, it seems plausible to state that it should be given to patients with whom other therapeutic approaches have failed However, in view of the unusually high success of the conditioned-reflex therapy, as compared with other kinds of therapy, a broader conception is justified — that is, all patients who are physically and psychologically eligible should actually have the opportunity to avail themselves of it The latter point of view will be even more acceptable if the working hypothesis of the autonomous, self-perpetuating, abnormal reflex of addictive drinking is kept in mind The contraindications, which have been listed elsewhere,¹⁰ are briefly as follows I Q markedly below 100, constitutional psychopathy, lack of intellectual or emotional ability to recognize the necessity of permanent abstinence, record of serious criminal offenses committed in a state of sobriety, combination of alcohol and drug addiction, and acute psychosis

Physical contraindications include disturbances of the cardiovascular-renal system, active tuberculosis of the lungs, active peptic ulcer and cirrhosis of the liver

EFFICACY

The efficacy of the treatment is demonstrated by the following statistics 282 patients have undergone the conditioned-reflex therapy since February, 1942, and 7 of these did not finish the initial series, the total thus being reduced to 275 Results have been verified, in most cases, by periodic, personal contacts in the form of weekly interviews, reinforcements, semimonthly abstinence-club meetings and, for patients living in remote parts of the United States and Canada, by correspondence, which is rechecked by social workers, local physicians, probation officers and relatives

Out of these 275 patients no follow-up information is available on about 30 patients, leaving a remainder of 245 Of these, 125 are still total abstainers This figure includes 9 who relapsed once and had to be retreated Of the 125 patients, 21 have been totally abstinent for six to seven years, 37 have been abstinent for five to six years, and 15 for four to five years The rest have been abstinent from one to three years

The over-all percentage of abstainers among the 245 patients is 51.02 These statistics purposely do not exclude patients who combined alcohol with drug addiction, patients who accepted the treatment not quite voluntarily, but under certain pressure from employers or their families, and patients whose chance for rehabilitation was impaired by factors beyond those stemming from alcohol addiction, such as poor working history, lack of trade or profession, criminal background or an occupation that exposes them continuously to alcoholic beverages, such as package-store owners, bartenders, butlers and businessmen who have to entertain

PSYCHOTHERAPEUTIC ASPECTS AND MECHANISMS

To consider the conditioned-reflex treatment a mere physiologic or drug therapy would be tantamount to considering only one of its aspects Like any other physiologic or drug therapy, only even more so, the conditioned-reflex therapy includes a considerable amount of dynamic psychotherapy As pointed out elsewhere¹⁰ and in the opinion of other authors,* alcoholic patients often suffer from feelings of guilt and inferiority The patient undergoing the conditioning against alcohol perceives the repeated exposure to the repulsive sight, smell and taste of alcoholic beverages with subsequent nausea as punishment and purification This procedure of atoning reduces and eliminates his feelings of guilt On a more superficial level the patients experience a feeling of heroic accomplishment This in itself is an excellent counterweight for their feelings of diffidence and inadequacy with all the subsequent self-criticism and self-hatred Thus, it seems reasonable to consider the conditioned-reflex therapy as a psychosomatic approach to a truly psychosomatic disease

SUMMARY AND CONCLUSIONS

The rationale, technic, risks, indications, contraindications, efficacy and psychotherapeutic aspects of the conditioned-reflex treatment as applied to 282 patients are discussed

A new conception of the autonomous character of alcohol addiction in relation to the underlying neurosis is offered Psychotherapeutic mechanisms involved in the conditioned reflex therapy are pointed out

*Bird¹¹ states "The alcoholic who always feels terribly guilty whether he admits it or not, often feels a need to be punished and being punished may lessen his guilt"

represent a contraindication for conditioned-reflex therapy. The initial series of the treatment involved seven injections with a total dose of 0.54 gm (9 gr) of injected emetine, followed by an additional injection of 0.15 gm ($2\frac{1}{2}$ gr) of injected emetine nine days later. During that whole period this patient did not display any tachycardia, drop in blood pressure, arrhythmia, gastrointestinal or neuromuscular side effects. Fifteen days after the initial series, the patient traveled to a neighboring state for some urgent business. For two days, he was exposed to relatively marked physical strain. Three days later he complained of weakness of the lower extremities, shortness of breath and occasional precordial distress. An electrocardiogram and clinical examination revealed sinus tachycardia. Five days later he was definitely better. His pulse was still 140, but the blood pressure rose to 110 systolic, 80 diastolic. Another five days later, the pulse slowed down to 110, eight days later it was 96, and the blood pressure was 125 systolic, 70 diastolic. Although the electrocardiogram still showed abnormalities, it also revealed progressive improvement in the condition of the myocardium. There was still gallop rhythm. From then on the blood pressure remained normal. The only abnormal sign—the gallop rhythm—disappeared finally three weeks later.

Another patient, an asthenic, fifty-year-old man with an asthmatic bronchitis and a positive blood Hinton reaction, felt, thirteen days after a total dose of 0.8 gm (13 gr), dizzy and lightheaded for one day. Aside from this side effect, he complained of muscular weakness and aching for twenty-three days.

Several hours after the first emetine injection of 55 mg a third patient, a slender, run-down, fifty-seven-year-old man, showed severe gastrointestinal and circulatory manifestations, such as severe, watery diarrhea, pallor, a very small, rapid pulse (120 per minute), cramps in both legs and cold extremities. Fifteen minutes after caffeine injection he felt more comfortable, and the pulse was 96 and better filled. The blood pressure was 120 systolic, 80 diastolic. The rest of the series of injections was well tolerated and provoked no immediate untoward reactions. However, a week after the end of the series, the patient complained of fainting spells and palpitations, shortness of breath, tachycardia and muscular weakness. An electrocardiogram showed auricular fibrillation. Rest in bed, digitalis and ammonium chloride brought the heart back to normalcy. From then on the patient was able to tolerate the additional reinforcements without any toxic manifestations.

Sometimes lack of judgment and restlessness, not at all a rare phenomenon in alcoholic patients, may prevent a patient in need of rest in bed from following medical advice. Such nonco-operation

may prove fatal, as the following case history illustrates.

A 35-year-old unusually obese man (weighing 241 lb), with a blood pressure of 106/76, negative liver tests and an electrocardiogram within normal limits, underwent the initial series of the conditioned-reflex treatment after recovery from a bout of drinking lasting 6 weeks. The total dose of injected emetine was 0.77 gm ($12\frac{3}{4}$ gr). He claimed that he was too restless to stay in bed during the days of the initial series and was even more restless after that. He insisted upon leaving the hospital only 2 days after completing the initial series and on resuming his occupation as a very active salesman.

One week after discharge from the hospital, tachycardia and gallop rhythm developed. Again, he refused hospitalization, for business reasons, for another 2 days. Finally, he returned to the hospital with complaints of general weakness and shortness of breath. Physical examination revealed a heart enlarged in all diameters, with the apical beat in the sixth interspace, the heart rate was 110 and regular, and the blood pressure 110/80. From then on the cardiac failure progressed rapidly. Approximately 12 hours after readmission the patient died.

Kattwinkel⁹ has recently reported an additional fatal case. Fortunately, such a fatal termination occurred in only 2 cases out of 282 treated, representing a mortality of 0.7 per cent.

To reduce to a minimum and, if possible to eliminate the risks of toxic manifestations altogether, three modifications are now applied. In the first place the initial series of injections consists now of only six, the total initial dose of injected emetine thus being reduced to 0.675 gm ($11\frac{1}{4}$ gr). Secondly, pilocarpine has been eliminated from the injectable emetine solution. Thirdly, the conditioned reflex therapy is applied only to patients who accept the plan of rest in bed and hospitalization for an additional four weeks after completing the initial series of treatments. The number of patients who have complied with this stipulation is so far too small to form a basis for conclusions. It has been reassuring, however, that no cardiovascular side effects have developed.

The primary research plan at the Washingtonian Hospital is either to modify emetine chemically or to substitute for it another suitable emetic, with the goal of preventing not only the cardiovascular complications but also the side effects.

A discussion of the efficacy of the conditioned-reflex therapy would be incomplete without mention of the question of recidivism. The relapse seems to be caused in some cases by external and in others by intrinsic factors. The first group may be benefited either by single reinforcements or by a full retreatment including the initial series. The prognosis for such patients is good, probably because of the very fact that it takes considerable maturity and determination to return for additional treatment.

One patient who relapsed largely for external reasons was a man in his forties, in a responsible position, who clearly realized the necessity for total abstinence from alcoholic beverages and who did his best to obtain it by undergoing a course of in-

dividual psychotherapy. After several failures to prevent relapses, his therapist referred him for conditioned-reflex therapy. When the patient completed his initial series of the conditioned-reflex therapy, he was advised to return four weeks later for his first reinforcement. Circumstances delayed his return by an additional three months. As it happened he was able to abstain from drinking for those four months, but when he again, for external reasons, postponed his second reinforcement he relapsed. He then accepted the suggestion of a full retreatment, and six years later was able to report that he was apparently completely cured.

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To consider the conditioned-reflex treatment a mere physiologic or drug therapy would be tantamount to considering only one of its aspects. Like any other physiologic or drug therapy, only even more so, the conditioned-reflex therapy includes a considerable amount of dynamic psychotherapy. As pointed out elsewhere¹⁰ and in the opinion of other authors,* alcoholic patients often suffer from feelings of guilt and inferiority. The patient undergoing the conditioning against alcohol perceives the repeated exposure to the repulsive sight, smell and taste of alcoholic beverages with subsequent nausea as punishment and purification. This procedure of atoning reduces and eliminates his feelings of guilt. On a more superficial level the patients experience a feeling of heroic accomplishment. This in itself is an excellent counterweight for their feelings of diffidence and inadequacy with all the subsequent self-criticism and self-hatred. Thus, it seems reasonable to consider the conditioned-reflex therapy as a psychosomatic approach to a truly psychosomatic disease.

SUMMARY AND CONCLUSIONS

The rationale, technic, risks, indications, contraindications, efficacy and psychotherapeutic aspects of the conditioned-reflex treatment as applied to 282 patients are discussed.

A new conception of the autonomous character of alcohol addiction in relation to the underlying neurosis is offered. Psychotherapeutic mechanisms involved in the conditioned reflex therapy are pointed out.

*Bird¹¹ states: "The alcoholic who always feels terribly guilty whether he admits it or not, often feels a need to be punished and being punished may lessen his guilt."

The therapeutic efficiency of the method available at the Washingtonian Hospital, the only American hospital specializing in the treatment of alcohol addiction, is considered very encouraging

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THE MANAGEMENT OF ABNORMAL UTERINE BLEEDING*

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EXCEPT for the stain of newborn females and the normal menstruation of constitutional precocity, all the rare cases of uterine bleeding during the period of childhood and preadolescence are but one manifestation of the precocious puberty associated with the following unusual conditions: certain cases of midbrain damage, Albright's disease, exceptional cases of tumor of the adrenal cortex, granulosa-cell tumor of the ovary and, very exceptionally, chorioncarcinomatous teratoma of the ovary. The observation of premature growth and development, then, is the signal for immediate investigation and possible operation. Uterine bleeding after the establishment of the menopause is due most often to intrauterine or ovarian neoplasms, or both, rarely to cancer or sarcoma in the myometrium or to tubal cancer and very rarely to intrinsic vascular disease in the uterus. Between the menarche and the menopause the definite causes of abnormal uterine bleeding are intrauterine tumors and infections, pathologic pregnancy, both intrauterine and extrauterine, retained products of gestation, submucous fibroids, some estrogenic tumors of the ovary, diseases impairing the ability of the circulating blood to clot, and ovarian dysfunction. Placental dysfunction is, of course, involved in the bleeding of pathologic pregnancy. Less clear-cut causes during this span of life are myometrial and subserous tumors, pelvic inflammations, endometriosis, retroversion of the uterus, nonestrogenic tumors of the ovary and uterine fibrosis, since these entities are often present without any abnormality of flow.

It is quite apparent that all the conditions listed — and the list is essentially complete — are, with the exception of infections, not the primary causes of

abnormal uterine bleeding. Nor are they the ultimate causes. They are intermediate causes whose primary etiologies are still unknown. As a result of the action of one or more of these intermediate causes, the ultimate factors, chemical and mechanical, that actually rupture blood vessels within the uterus come into play in an abnormal way.

MANAGEMENT

According to the indications of present knowledge most, if not all, of the complications of pregnancy and the uterine bleedings that sooner or later accompany them are due to placental dysfunction. Because of ignorance concerning primary etiologies, the assumption has been made for years that any disease or disorder anywhere in the body may somehow lead to placental dysfunction. The improvements from better prenatal study and care have justified this assumption. Also because of ignorance concerning specific primary etiologies, it is assumed that any disease or disorder may be an etiologic factor and as such may make ovarian dysfunction a cause of abnormal flowing in the nonpregnant woman, in addition to, or in the absence of, any of the causes listed above. This is the reason for including in the long-range management of abnormal uterine bleeding the study and treatment of the whole patient, even though the beneficial effects may not become at once apparent. Especial and immediate attention is, of course, directed not only to the uterus and adnexa but also to the vulva, vestibule, urethra, vagina and cervix for sources of bleeding. Some women are, understandably, still averse to being examined while flowing. Tragic delays too often result. Their objection is easily overcome when the dangers of delaying the diagnosis and prescribing medication without a diagnosis are explained.

Since it would be futile in a presentation of this sort to attempt a discussion of pathological physiol-

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ogy, diagnosis and treatment in relation to all the conditions concerned in abnormal uterine bleeding, a few points under the headings of surgery, radiation and the use of hormones are considered

Surgery

During the early teens operation is practically never necessary, in either the diagnosis or the treatment of this complaint, which is usually due to ovarian dysfunction of undeterminable cause and responds to the progesterone therapy described below. Some of these young women will have recurrent ovarian dysfunction that can be controlled by progesterone and finally ceases developing. Occasionally, however, one of them continues to have recurrent dysfunctional flowing, and cancer of the endometrium will be found during the twenties or early thirties. Drs Arthur T Hertig and Sheldon C Sommers will soon report 16 such patients whose endometrial hyperplasia became malignant. The patient with persistently recurring dysfunctional bleeding, then, requires particular attention in the matter of follow-up study and endometrial biopsy.

From the age of eighteen on, surgical diagnostic and therapeutic procedures are, of course, increasingly indicated for a great variety of situations of which abnormal uterine bleeding is a sign. This brings me to an aspect of conservative pelvic surgery concerning which I have a strong conviction. All gynecologists have the relatively frequent experience of seeing patients with this complaint who have had previous operations consisting of the excision of both tubes or bilateral tubal ligation, with or without ovarian surgery. These women are usually over thirty-five years old. A uterus capable of only one function, menstruation, yet still capable of being the source of serious or very serious trouble has been conserved. At the Free Hospital for Women 35 patients with cancer of the cervix and 6 with endometrial cancer have had these operations. In addition, 60 to 100 women with bleeding associated with fibroids, chronic pelvic inflammation, polyps and ovarian-endometrial dysfunction who have had these operations are treated each year. The operations had been performed with the mistaken idea, which was due to earlier teachings, that menstruation must be important for health, even in the absence of the ability to conceive. There is no evidence, however, that menstruation has any physiologic value except in relation to fertility. On the contrary, there is ample evidence of its being indeed "the curse." My own conclusion from available knowledge is that it is an expression in the non-pregnant woman of a process that must be very important in the physiology of pregnancy. This process is decidual necrosis, which, according to Dr Hertig, is a constant feature of human gestation. And certainly amenorrhea in itself is in no way ever harmful. Therefore, it is my firm conviction, and I submit it for serious consideration, that when opera-

tions involving sterilization are required, the continued health of these patients is more certainly assured by the removal of the uterus. This prophylaxis eliminates not only menstruation with all its attendant unpleasantness, including premenstrual tension, which is so common to all ages, especially after thirty-five, but also the potential source of tumors, benign and malignant. In retrospect it would have been life saving for many women. It almost completely eliminates soreness of the breasts, and fibrocystic changes in the breasts may disappear after it. I am advocating hysterectomy only in this limited group of patients and not the removal of any ovarian tissue except as indicated in the individual case. When normal ovaries are conserved, menopausal symptoms do not occur prematurely. There are only three exceptions to my proposal. One is that some women, though none in my experience, consider uterine bleeding an indispensable manifestation of their femininity. Another is tubal interruption at the time of cesarean section. The third is when serious systemic illness requires limiting the amount of pelvic surgery to the necessary minimum. In connection with the question whether the hysterectomy should be complete or supracervical, I simply state that, in addition to those whose cancers of the cervix are missed at the time of the incomplete operation, at least 1 of every 100 women so treated will develop this disease some time later. Moreover, 75 per cent of patients with cancer of the cervical stump die of the disease.

After the establishment of the menopause any bleeding from the uterine cavity indicates the presence of a surgical condition. There is no place for the use of hormones in the treatment of postmenopausal uterine bleeding. The condition may be nothing more than an endometrial polyp, which is likely to be found with the placental forceps or a clamp if missed by the curet. A palpable ovary in a postmenopausal patient is always pathologic. Even when no ovarian enlargement can be felt, the finding of hyperplastic endometrium signifies neoplastic ovarian activity. This may be benign but is always potentially malignant, as is the endometrium stimulated by it.

Radiation

The majority of women sterilized by radiation for abnormal bleeding associated with benign conditions, such as ovarian dysfunction and fibroids that are not submucous, get along very satisfactorily so far as later serious or disturbing pelvic troubles are concerned. That radiation is known to provide no immunity to the later development of genital cancer is no contraindication to its employment, for cancer might have developed anyway. On the other hand, according to recent studies, irradiation itself is probably carcinogenic in the susceptible woman. On occasion, a granulosa-cell tumor, thecoma or "thecomatosis" of the ovary appears to have its

etiology in previous irradiation. Also on occasion, atresia of the upper vagina or cervix from this treatment may prevent malignant growths at higher levels from manifesting themselves until too late. In other words, enough patients do have pelvic trouble sooner or later, even up to thirty years, after radiation for benign conditions to make one wish that the original therapy had been surgical or had consisted of temporizing with medical management of the bleeding until ovarian function had become adjusted. Therefore, in general, it seems better to treat fibroids surgically, at the same time avoiding unnecessary castration in younger women. Similarly, it seems better in general to omit radiation for dysfunctional uterine bleeding and, instead, to employ surgery in selected cases and hormones in the others. By selected cases I refer to quite a few women between the age of thirty-five and the menopause who have dysfunctional bleeding, and often premenstrual tension as well, and also prolapse and vaginal relaxation with symptoms therefrom. Many of these are best treated by vaginal, or complete abdominal, hysterectomy without removal of the ovaries, along with reconstruction of the vagina. In the absence of the uterus, simple ovarian dysfunction is harmless, causing little or nothing in the way of symptoms and no signs.

Hormones

Of the available hormones, progesterone and estrogen can be counted upon for predictable, immediate results in the control and regulation of dysfunctional uterine bleeding. Of the various ways of administering these ovarian hormones, I have found the following most effective:

For the patient who has been flowing more than seven days, even for months, at the time the diagnosis of dysfunctional uterine bleeding is made 25 mg of progesterone is injected intragluteally daily for five days during which the flow will slacken or cease. Two to four days after the last injection of this progesterone series a menstruation, often profuse, will ensue, ending in less than six days. The patient should be warned that the induced menstruation is the necessary evil of this efficient treatment. Normal cycles are likely to follow, for a time at least, but to make more certain of this result it is well to repeat the progesterone series at least once, starting eighteen to twenty-one days from the onset of the induced menstruation. Should irregular bleeding persist between progesterone-induced periods it is certain that some pathologic condition besides an abnormally functioning endometrium is inside the uterus. In other words, the failure of progesterone to be immediately therapeutic, when given as de-

scribed, points to an incorrect diagnosis and the necessity of investigation under anesthesia at once.

For the patient whose cycles are of normal length but whose bleeding is profuse, or continues up to eight days, and who often has premenstrual staining as well, the simplest therapy is the oral administration of estrogen starting with the onset, or during the first two days, of the period. Estrone sulfate, in divided doses totaling 10 mg daily, is taken for twenty-five days. To reduce expense, stilbestrol in daily doses of 5 mg, 10 mg or even 25 mg may be taken, on retiring, instead of estrone sulfate. Both of them may cause malaise in some women, in others a sense of well being is produced. The occurrence of bleeding between the sixth day and the end of estrogen treatment indicates the presence of some undiagnosed condition within the uterus. Two to six days after the cessation of medication uterine bleeding will begin. Though not profuse, it occasionally lasts up to eight days. Thereafter, normal catamenia may or may not ensue. Should excessive flow again appear early in a cycle, the estrogen treatment may be started at once and continued again for twenty-five days.

For this type of abnormal bleeding the progesterone series also has a place. If elected, it should be started between the eighteenth and twenty-first days of the cycle. Although in some women the ensuing catamenia may be profuse, it will not last so long. Moreover, there is a greater chance that normal catamenia will follow than after the estrogen treatment.

For the woman whose cycles are disturbingly shortened, whether or not her bleeding is profuse or prolonged, the progesterone series is begun eight days before the expected onset of a period. Or the estrogen treatment is given beginning at the start of flow. Here again, uninterrupted bleeding during estrogen treatment or following a post-progesterone menstruation is indicative of an incomplete diagnosis.

CONCLUSION

The management of abnormal uterine bleeding is fundamentally similar to the management of any other sign or symptom. It involves the diagnosis and treatment of definite and possible causes, the direct treatment of the complaint in the absence of determinable causes, and the therapy, so far as possible, of all other discoverable abnormalities. I am reminded of the illustrious statement by Dr. Francis W. Peabody that "The secret of the care of the patient lies in caring for the patient." I take the liberty of paraphrasing it as follows: the secret of the care of the patient lies in taking care of the whole patient.

MEDICAL PROGRESS

RESUSCITATION (Concluded)*

SIDNEY C WIGGIN, M D,† PETER SAUNDERS, M D,‡ AND GEORGE A SMALL, M D §

BOSTON

ASPHYXIA NEONATORUM

Asphyxia neonatorum is the most frequent emergency requiring resuscitation that is encountered in the delivery room. It is characterized by the absence of spontaneous effective respiration. The mechanism of the development of this type of respiratory arrest differs from those classified in the previous section, but the resultant pathological physiology has much in common with them.

The difference between asphyxia neonatorum and cardiorespiratory arrest is that in the latter both respiration and circulation cease and must be maintained artificially, whereas in asphyxia neonatorum, it is rare for the heart to stop beating and it is only the respiratory arrest that requires artificial correction. That this basic difference is generally accepted is well substantiated by the fact that artificial respiration in relation to asphyxia of the newborn is extensively discussed in the literature, while mention of cardiac resuscitation of the newborn is conspicuously rare. It is obvious that the newborn infant who has both respiratory arrest and cardiac arrest has declined to a state that is irreversible. As in all other cardiorespiratory accidents, the indispensable primary principle in the treatment of asphyxia neonatorum is the urgent necessity of delivering oxygen to the tissues before anoxic changes become irreversible. The most prominent anoxic manifestations are cardiac arrest and damage to the brain.⁹⁷

Pathological Physiology

The pathological changes in various organs contingent upon the anoxia in asphyxia neonatorum are typified by congestion of blood vessels, interstitial edema, diapedesis of blood cells, hemorrhages and necrosis of tissues.⁹⁸ In cases in which anoxia does not advance to the point of cardiac arrest the greatest danger is damage to the brain. Russ and Strong⁹⁹ indicate that prolongation of anoxia for more than two minutes after delivery of an infant will cause serious cerebral changes. Numerous reports and experiments prove that brain damage

can occur despite successful resuscitation and can result in crippling sequelae such as mental inferiority, diminution of ability to learn and mental dullness.¹⁰⁰⁻¹⁰¹ Studies of groups of children who had suffered varying degrees of asphyxia neonatorum revealed a high incidence of abnormal cerebral function, low intelligent quotients, retardation in later life and markedly affected behavior patterns often to a point incompatible with normal living, 26 per cent of the children were morons, imbeciles or idiots.¹⁰²⁻¹⁰⁴ These observations emphatically indicate that the major damage to the brain of the newborn infant from anoxia is manifested in later developmental abnormalities.

The outstanding pathological lesion at autopsy in cases of asphyxia neonatorum is the complete atelectasis of the lungs, which are airless, without crepitation and are a compact solid viscus having a fleshy parenchyma.¹⁰⁰⁻¹⁰⁵ Partial atelectasis may exist for long periods after respiration begins.¹⁰⁷

The alterations in blood chemistry in asphyxia neonatorum are not discussed, the reader is referred to the respective section of the collective review on this subject written by Little and Tovell.¹⁰⁰

Etiology

Little and Tovell¹⁰⁰⁻¹⁰⁵ point out in two excellent reviews on the subject of asphyxia neonatorum that the complete syndrome is usually the result of a combination of several of the numerous etiologic factors rather than any one factor in itself. They catalog the etiologic elements in three groups: those pertaining to the mother, those pertaining to the products of conception, and those pertaining to the labor and delivery.

There is a significant increase in the incidence of asphyxia of the newborn when the mother's age exceeds forty years.⁹⁹⁻¹⁰⁹ when the mother is a primipara or multipara after the eighth pregnancy.¹¹⁰⁻¹¹¹ and when the mother's health has been adversely influenced by cardiac disease, pulmonary disease, genitourinary infection, gastrointestinal disorders, metabolic disturbances and toxemia of pregnancy.¹¹¹⁻¹¹⁵

Abnormalities of the products of conception related to low viability of the germ plasm, immaturity of the fetus, congenital defects such as malformation of the respiratory and circulatory systems, and congenital debilities such as syphilis and erythroblastosis fetalis adversely affect the inci-

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dence of neonatal asphyxia^{107, 116 119} Furthermore, the role of unfavorable position of the fetus in the uterus — particularly breech, transverse and occiput posterior presentations — is of appreciable significance

The factors pertaining to the labor and delivery that are regarded as of tremendous importance by Little and Tovell in unfavorably influencing the occurrence of asphyxia neonatorum are as follows: duration and type of labor — long, dry labor or long difficult labor associated with cephalopelvic disproportion^{113 114 120}, induction of labor with drugs such as quinine and Pituitrin^{111 112 120 121}, complications of labor — infarction of the placenta, low insertion of the placenta, placenta praevia and premature separation of the placenta, anoxia to the fetus originating in impaired circulation in the cord and anoxia to the fetus of uterine origin^{99 113 115 122 123}, type of delivery — version and extraction, high forceps, breech extraction, mid forceps, cesarean section and low forceps without episiotomy^{110 114 116 122 124}, and analgesic drugs and anesthetic agents and methods^{108 113}

In a series of 143 infants who died in the neonatal period from asphyxia and atelectasis, Roberts¹²⁵ found the close relation between intracranial damage coincident to difficult labor and this type of death very prominent, 55 of these infants evidenced intracranial damage. Confirmation of this observation is contributed by Russ and Strong,^{126 127} who also call attention to the importance of debris in the newborn infant's trachea as a cause of respiratory difficulty, particularly when delivery has been accomplished by cesarean section

Diagnosis and Classification

The diagnosis of asphyxia neonatorum is made by the simple observation that respiration is absent. Ascertaining the concomitant degree of anoxia is not so simple and is of major importance. Many classifications have been recorded to describe the conditions produced by progressing oxygen deficiency¹²⁸⁻¹³². The following classification offered by Flagg,¹³³ in which physical findings are the basis for diagnosis, is the one generally accepted and is the most practical from the therapeutic point of view

1 *Stage of Depression* baby does not breathe well, tendency to duskeness and recurring cyanosis, respiration free, but slow and irregular

2 *Stage of Spasticity* irregular, gasping, or shallow respiration occurring at long intervals, marked cyanosis of mucous membrane with blotching of skin or general pallor, the baby's gums close over the gloved fingertip, reflex reaction to suction of the pharynx, such as movement of facial muscles or extremities, if pharynx is exposed, pharyngeal reflex is sluggish or active and the glottic reflex is active

3 *Stage of Flaccidity* respiration occurs at long intervals or cannot be demonstrated, cyanosis or pallor, complete flaccidity of musculature, all muscle tone gone, jaw

completely relaxed, no resistance to suction or exposure of the pharynx, fluid is found in hypopharynx, apex beat may or may not be demonstrable

Prophylaxis

Since many of the etiologic factors capable of abetting the occurrence of asphyxia neonatorum are to some extent under the control of the physician much can be done in the way of preventive measures to reduce the incidence of this condition. Factors that are partially controlled by the physician are listed as follows by Little and Tovell¹⁰⁸: the health of the mother, congenital disease of the fetus, presentation and position, and the duration and type of labor and delivery. The last of these has further been highlighted by an analysis by Russ and Strong⁹⁹ of more than 1000 cases of asphyxia neonatorum enabling them to draw the conclusion that the prolongation of labor in association with a traumatic type of delivery is by far the most notable single cause. The emphasis upon the importance of conscientious and intelligent observation during the conduct of labor and the election of the safest and most suitable methods of delivery as vital prophylactic measures in asphyxia of the newborn is apparent.

Within the complete control of the physician are the induction of labor and the use of analgesics and anesthetics. The latter is important enough and controversial enough to demand some elaboration. Little and Tovell¹⁰⁸ have made a comprehensive study of this subject that enables them to conclude that there is a close causal relation between an increase in asphyxiated infants at birth and the use of analgesic and anesthetic drugs, in that every one of them may increase the incidence of this complication. They endorse and commend the approach of Grantly Dick Read to the problem of relief of pain in childbirth. This method is one in which a mental prophylaxis against fear is initiated in the expectant mother and renders the use of drugs unnecessary in the majority of cases.^{134 135} Read's^{136 137} practices have been gaining widespread recognition during recent years.

Though sounding a warning, Little and Tovell¹⁰⁸ do not condemn modern analgesia and anesthesia, "for the fault lies not so much in the drugs but in their methods of application." They signify that the following pharmacologic principles must be scrupulously adhered to when analgesics and anesthetics are administered: "each patient must be evaluated and treated on an individual basis, the dosage of the drugs administered must be the minimal effective dose, the physician must be in constant attendance to evaluate the effects of the agents on the woman in labor, cognizance must be taken of the presence of other factors besides those of analgesia and anesthesia that may tend to produce asphyxia neonatorum, and the use of

analgesics and anesthetics must be modified accordingly”

Treatment

In the treatment of asphyxia neonatorum there are two objectives to *deliver oxygen to the tissues* — as in any case of cardiorespiratory arrest, the saving of life and the avoidance of permanent brain damage will depend upon the successful execution of this principle by ventilation of the lungs, and to *protect the infant from harmful influences* — by institution of measures that safeguard normal physiology

Whereas the aims in the treatment of cardiorespiratory arrest are achieved one after the other, in the treatment of asphyxia neonatorum both propositions must be carried out simultaneously

Since asphyxia neonatorum is not complicated by cardiac arrest there is no need for the maintenance of circulation by cardiac massage

The first aim of resuscitation of the newborn is delivery of oxygen to the alveoli of the lungs by either stimulation of spontaneous respiration or artificial respiration

Stimulation of spontaneous respiration It must be borne in mind that this approach is justified only in the first stage of asphyxia, that of depression, in which the baby does not breathe well, respiration is slow and irregular. Gentle cutaneous friction, passive movements of the extremities and catheter aspiration of the nose, mouth, and pharynx are the acceptable procedures for this purpose^{115 123 141}

Artificial respiration If the infant does not breathe within thirty seconds of severing of the cord, artificial respiration must be instituted regardless of the stage of asphyxia^{99 115}. The most efficient method of applying artificial respiration to the newborn appears to be that performed by the employment of the Kreiselman resuscitator¹⁴²⁻¹⁴⁶. This mechanical resuscitator supplies an intermittent flow of oxygen under a controllable positive pressure, which may never exceed 15 or 16 mm of mercury. Oxygen is administered thirteen to fifteen times a minute, two or three seconds being allowed for inflation and two seconds for passive deflation, a positive pressure of 12 mm of mercury is applied at the outset for inflation of the lungs, and this may be increased to 14 or 15 mm. In the newborn this amount of positive pressure will not cause the chest to rise in the inspiratory phase because the lungs expand in a patchy distribution and it may take a long time for them to be thoroughly inflated. As Kreiselman¹⁴⁷ avers, the machine should be at hand in perfect working order for every delivery, and personnel expert in its use should be present.

If these conditions cannot be fulfilled and a simpler, immediately available means of administering artificial respiration must be resorted to, mouth-

to-mouth insufflation is considered the next choice^{78 107 142 148 151}

Disadvantages associated with this method are that it does not supply 100 per cent oxygen, there is the danger of the creation of excessive intrapulmonic pressure, which may cause fatal emphysema or pneumothorax, there is the possibility of overdistingending the stomach and rupturing it, and the procedure may lead to infection of the infant or of the operator¹⁵²⁻¹⁵⁷

Other means of artificial respiration employing resuscitators of the “suck and blow” type have been commended and condemned^{120 129 158-164}. Infant respirators of the Drinker type seem to have little practical value¹⁶⁵⁻¹⁶⁹

The dangers of excessive positive pressure mentioned above are present with all types of mechanical resuscitators, but they appear to be least likely with the Kreiselman apparatus, which provides the most adaptable means of positive pressure control¹⁷⁰. Finally, manual methods of artificial respiration in asphyxia neonatorum are observed to have no physiologic basis and are therefore of no value in the resuscitation of asphyxia of the newborn^{183 157 171-173}

The establishment and maintenance of a free air passage should be considered a part of the technic of artificial respiration. It is obvious that, without a free airway, oxygen cannot reach the alveoli of the lung. Gentle catheter aspiration of the nares, mouth, pharynx and, when necessary, the trachea and upper bronchial tree is advisable to remove aspirated material such as amniotic fluid, meconium and cellular debris, which may be the source of obstruction^{151 153 159 165 170 174}. Placing the baby in a head-down position helps serve the same purpose of draining material from the air passage, 15 to 30° of Trendelenburg position is considered optimal^{120 153 170}. In cases in which asphyxia has advanced to the stage of flaccidity, the collapsed glottic structures will produce obstruction of the airway. To obviate this obstruction, tracheal intubation is mandatory^{129 133 139 141 175 178}. The need for considerable skill in performing this procedure without trauma to the larynx is emphasized^{101 149 174}

The manipulations necessary to the establishment and maintenance of a clear airway are performed repeatedly as needed in conjunction with artificial respiration but in such a manner that artificial respiration is interrupted for only very brief periods. Performance of the initial aspiration of the upper respiratory tract is advisable the moment the head has been delivered and before the umbilical cord has been clamped^{101 133}

Formerly, the use of carbon dioxide was advocated as a stimulant to respiration in the resuscitation of asphyxia neonatorum, at present the use of carbon dioxide is considered useless or even harmful¹⁷⁹⁻¹⁸³

The status of drugs in the treatment of asphyxia neonatorum is identical with that of carbon dioxide or with that of drugs in the treatment of cardio-respiratory arrest, epinephrine, alpha lobeline, Pituitrin, camphor, coramine, picrotoxin, Metrazol, caffeine and strychnine have been proposed for consideration or have enjoyed the commendation of a number of observers^{150 157 174} More recently, the consensus is that they are likely to do more harm than good^{140 162 173}

The second aim of resuscitation of the newborn infant — that of maintaining normal physiology — is best furthered by scrupulous adherence to two simple principles. The first of these is the minimal handling of the infant to reduce the possibilities of shock, visceral lacerations and cerebral hemorrhage. There appears to be little justification for such "archaic methods of man-handling" as the Schultze giant swing, hot and cold tubbing, sprinkling the skin with ether, vigorous spanking, pummeling, dilating the anal sphincter and penile dorsal slit^{100, 120 172 184} Suspension by the feet to promote drainage of the respiratory tract, as formerly advocated, may aggravate the danger of cerebral hemorrhage. This suspended position is best avoided, and the optimal position of 15 to 30° Trendelenburg, as indicated above in the discussion of maintenance of a free air passage, should be utilized.

The second principle is immediate warmth. The importance of the retention of normal body temperature has been stressed^{99, 100 147} The practical importance of this measure has not been affected by theoretical objections¹⁸⁵

These essentials must be observed from the moment of birth throughout the period in which the newborn infant requires resuscitation.

Russ and Strong⁹⁹ believe that "the after-care of the newborn resuscitated baby is of equal importance to that of the resuscitation itself." This care includes preservation of oxygen physiology by inhalational therapy, close observation, placement in an incubator, withholding of feeding and the administration of a stimulant if necessary^{99 115 126 127}

* * *

The neonatal period is the most hazardous in life, here the mortality rate exceeds that of any other time, and the danger of permanent central-nervous-system damage is ever present¹⁴⁷ The persistent use of many faulty practices in the treatment of neonatal asphyxia may be an important factor contributing to fetal and neonatal mortality rates, which have improved but little during the past century^{107 133}

Although, in practice, resuscitation of the asphyxiated newborn infant remains primarily the province of the obstetrician,¹²⁶ in the words of Little and Lovell¹⁰⁸ "The anesthesiologist has come to join the obstetrician in being responsible not only for the safe and painless labor of the mother but, also,

for the safe deliverance of her infant, including, when necessary, the resuscitation of that infant."

ASPHYXIAL ACCIDENTS OUTSIDE THE OPERATING ROOM AND THE DELIVERY ROOM

The number of causes that may lead to asphyxial accidents in places other than the operating and delivery rooms is large and varied. Of these, the most important are inhalation of gases such as carbon monoxide, — illuminating gas and engine exhaust, — industrial gases — chemical, mine, refrigerants, smoke and chemical fumes, drowning, electrocution, drug poisoning from hypnotics, narcotics, sedatives and alcohol, and mechanical obstruction to respiration from smothering, strangulation, compression of the chest and choking — aspiration of foreign material and disease in the respiratory tract such as infection, tumor or allergy^{112 155 157}

In any of these conditions interruption of the oxygenation of the tissues is induced by either interruption of pulmonary ventilation — such as that which occurs in drug poisoning and electrocution, when the respiratory center is paralyzed, or as in drowning and mechanical obstructions of air passages, when effective ventilation becomes impossible, or interference with the oxygen-carrying power of the blood — as in carbon monoxide or nitrite poisoning, or finally arrest of the capacity of cells for utilizing oxygen (histotoxic anoxia) — as in cyanide poisoning¹⁰⁷

Although not of such vital significance as the lack of oxygen in asphyxial conditions, the retention of carbon dioxide in the blood contributes appreciably to the resultant asphyxial syndrome^{188 189}

When electrocution is the etiologic factor in an asphyxial accident, the respiratory arrest may be complicated by concurrent cardiac arrest¹²³

The location of asphyxial accidents has a notable bearing on their outcome¹⁹⁰ Obviously, the facilities available for resuscitative therapy are more immediately accessible in the emergency room of the hospital, the first-aid station or the doctor's office than in the home, at the roadside or river bank or in the field. Of equal significance is the personnel immediately available for initiation of life-saving measures, there can be no comparison between the effectiveness of the doctor or adequately trained first-aid technician and that of the casual passerby or inadequately informed lay person.

The classification of the stages of asphyxia given above in the section on asphyxia neonatorum is applicable to most of these asphyxial accidents. In the majority the initial stage is characterized by depression, which is followed by a period of struggle associated with spasticity and, finally, the third stage, in which there is complete flaccidity^{128 133}

A discussion of the pathological physiology, symptomatology, prophylaxis and special problems related to any one of these accidents, although fundamentally important to the physician, has been

omitted from this presentation. Most of this information may be obtained from Flagg's book on resuscitation.¹⁸³

Treatment

In the treatment of accidents of asphyxiation, it is imperative that two goals be attained: immediate delivery of oxygen to the alveoli of the lungs by artificial respiration, and support to the circulation, which is failing from anoxia.

Artificial respiration In accentuating the great importance of the time element in resuscitation, Comroe and Driggs¹⁸⁵ list the following basic principles that must be adhered to regardless of the nature or place of the accident: "The most immediately available method must be employed instantly" and "as soon as possible the most efficient method of artificial respiration should replace the emergency measure."

If, when a victim of an asphyxial accident is encountered, there are no facilities at hand for providing resuscitation, which is most often the case, the only method immediately available is manual artificial respiration.^{69 128 191} Of the several methods the generally approved technic is that of Schaefer, which employs rhythmic compression of the lower thorax with the patient in the prone position.^{34 192 193}

The manual methods of artificial respiration, even though properly executed, do not provide sufficient respiratory exchange and should not be regarded as definitive but only as a temporary emergency measure.^{188 194-197}

The means of providing efficient artificial respiration to replace the emergency manual procedure include the following:

Rhythmic inflation of the lungs by use of a mechanical apparatus Of these the simple and small bellows-type device introduced by Kreiselman appears to offer definite advantages in that it accomplishes adequate pulmonary ventilation with air or oxygen, when it is available, it is compact, inexpensive and easily portable.¹⁴⁸ Other more elaborate machines for performing artificial respiration are obtainable on the market. Among these are the E and J, the Emerson, B-K, Davis, and H and H inhalators and resuscitators.^{129 133 195} They supply 100 per cent oxygen or a mixture of oxygen and carbon dioxide by either alternating positive or negative pressure from 15 to 25 mm of mercury. These machines are mechanically accurate but not quite so easily transportable.

The tilting method of Ege This method utilizes the tilting of the patient 45° in the head-up position (inspiratory phase), followed by a sharp reversal to 45° in feet-up position (expiratory phase). Respiratory exchange is produced by movements of the diaphragm in response to ascent and descent of the abdominal viscera with the sudden changes in position. The respira-

tory exchange afforded is better than that with manual methods, and although this means of artificial respiration is highly recommended, its efficiency does not approximate that of rhythmic inflation of the lungs by apparatus employing positive pressure. Further limitations are difficulties encountered in transporting or improvising the necessary apparatus. Ege's tilting method does contribute two features of value irrespective of its utility for artificial respiration. These are a beneficial massaging effect on the heart and the facilitation of drainage from the respiratory tract when it is used in the treatment of a victim of drowning.^{78 185 199}

Insufflation of oxygen with endotracheal intubation Insufflation of oxygen without respiratory excursions of the chest can provide oxygenation and might be employed in the treatment of asphyxia, however, it should not be used for more than a few minutes without the addition of rhythmic manual compression of the chest because the accumulation of narcotic concentrations of carbon dioxide will occur.^{185 200-202}

The establishment and maintenance of an unobstructed airway is a prerequisite of artificial respiration. None of the methods of performing artificial respiration will be effective without patency of the air passage. It is because automatic machines for supplying artificial respiration are so often employed with disregard to respiratory obstruction that they have been generally considered both hazardous and unscientific.¹⁸³ The same observation is applicable to other methods of artificial respiration.

One of the most frequent causes of interference with the free passage of air is an abnormal position of the pharyngeal structures as represented by the backward displacement of the tongue, which is more prone to occur in the supine position than when the victim is face down.¹⁹⁵ Regardless of the type of artificial respiration employed, the operator must be constantly on the alert for this possibility.^{183 181} Proper support of the jaw, pulling the tongue forward and insertion of nasal or oral "airways" are simple measures and may contribute to overcoming the difficulty, on the other hand, they may be inadequate.^{112 116} The passage of an endotracheal tube, which requires experience and often a good deal of time, assures a patent respiratory passage and is urged by Flagg for all patients who have declined to the stage of flaccidity.^{183 203}

Other causes of respiratory obstruction are occlusion by some foreign body or by a pathologic deformity of the respiratory tract. These may be the initial causes of asphyxial accidents as illustrated by the example of a victim of choking.^{107 133 156} In the event of a pathologic deformity or inhalation of a foreign body, when simple measures such as suspending the victim head down and finger exploration of the throat have failed to

dislodge the obstructing material, emergency tracheotomy or intubation will be required ^{133 181}

Several factors such as the nature of the obstruction, the stage of asphyxia, the available facilities and familiarity with these technics determine whether tracheotomy or endotracheal intubation should be resorted to. Gross deformity of the glottis may render intubation impossible. The victim in the stage of spasticity is unsuited for intubation ¹³³. Patients in the first or second stage of asphyxia who have an appreciable respiratory exchange irrespective of the nature of the obstruction may be given oxygen with maximum available intermittent positive pressure synchronized to the patient's respiration during transportation to the nearest hospital, where immediate tracheotomy, laryngoscopy, bronchoscopy or intubation may be performed ^{133 181 201 208}

After tracheotomy, if the resuscitating apparatus can be attached to the tracheotomy-tube opening so as to be airtight, oxygen under intermittent positive pressure should be administered. If it is not possible to supply such an airtight system, a constant flow of oxygen should be insufflated through the tracheotomy opening while manual artificial respiration is simultaneously applied ^{107 133 181 204}

The causes of respiratory obstruction enumerated above may be further aggravated by aspiration of regurgitated gastric contents or other fluids and by the presence of excessive secretions. Brief and repeated catheter suction and postural drainage of the patient to remove these products should be utilized as necessary ^{107 133 181}

The gas used for artificial respiration should always be 100 per cent oxygen except in carbon monoxide poisoning ²⁰⁵⁻²⁰⁸. It has been demonstrated that with the addition of 5 to 10 per cent of carbon dioxide to the inhaled atmosphere, the elimination of carbon monoxide will be faster and the availability of oxygen to the tissues will be increased ^{107 209-211}

The second aim of resuscitation in asphyxial accidents—that of providing support to the failing circulation—includes measures to combat shock and stimulate heart function ^{212 214}

If facilities permit, fluid therapy should be administered intravenously, and measures by which the venous return to the heart can be increased, such as the Trendelenburg position, raising the legs to the vertical position ("autogenous transfusion") and application of tourniquet to the extremities, should be utilized ²¹⁵⁻²¹⁹. Normal body temperature should be maintained, but care must be taken not to overheat the patient ²²⁰

Employment of drugs that stimulate circulation such as epinephrine, ephedrine and related amines should be resorted to only if complete oxygenation has been established ^{215 218 221}

During the aftercare when the patient has regained spontaneous respiration, further inhalation

and fluid therapy, supervision of a free respiratory exchange, attention to bladder and bowel functions and the maintenance of body temperature are in the realm of general nursing care but are essential components of thorough treatment

* * *

A trend that had developed over the past twenty years has led to an undesirable situation regarding asphyxial accidents. This situation is characterized by overzealous activities of lay rescue squads and at the same time a lack of professional interest in problems of resuscitation on the part of the physician. Insufficient essential knowledge of the anatomy of the respiratory tract, physiology of respiration, pneumatology, physiology of anoxia, pathological physiology and diagnosis of asphyxia is an obvious limitation to the capabilities of the lay rescuer. That this limitation is often not appreciated is evidenced by the calls to lay rescue squads that originate even from the operating and delivery rooms. The attitude of the medical profession frequently implies that the treatment proffered by the mechanical performance of the lay squad, aided by the inhalator, leaves nothing more to be desired ¹³³

The resolution by the American Medical Association to encourage instruction of medical students and postgraduates in pneumatology and in the treatment of asphyxial accidents, the activities of the Society for the Prevention of Asphyxial Deaths, Incorporated, and the inclusion of resuscitation as a basic subject in the specialty of anesthesiology, along with other efforts on the part of the medical profession, are laudable measures for the improvement of the situation ^{222 223}. It is hoped that in the future, in the words of Flagg ¹³³ "When the average physician looking upon impending asphyxial death is shocked into a realization that here and now is the supreme test of his life-saving skill as a physician, resuscitation will cease to be relegated to the care of those lay groups whose services have been and continue to be a bridge to span the period between helplessness and adequate medical care."

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dislodge the obstructing material, emergency tracheotomy or intubation will be required^{133 181}

Several factors such as the nature of the obstruction, the stage of asphyxia, the available facilities and familiarity with these technics determine whether tracheotomy or endotracheal intubation should be resorted to. Gross deformity of the glottis may render intubation impossible. The victim in the stage of spasticity is unsuited for intubation.¹³³ Patients in the first or second stage of asphyxia who have an appreciable respiratory exchange irrespective of the nature of the obstruction may be given oxygen with maximum available intermittent positive pressure synchronized to the patient's respiration during transportation to the nearest hospital, where immediate tracheotomy, laryngoscopy, bronchoscopy or intubation may be performed.^{133, 181 204-206}

After tracheotomy, if the resuscitating apparatus can be attached to the tracheotomy-tube opening so as to be airtight, oxygen under intermittent positive pressure should be administered. If it is not possible to supply such an airtight system, a constant flow of oxygen should be insufflated through the tracheotomy opening while manual artificial respiration is simultaneously applied.^{107, 133 181 201}

The causes of respiratory obstruction enumerated above may be further aggravated by aspiration of regurgitated gastric contents or other fluids and by the presence of excessive secretions. Brief and repeated catheter suction and postural drainage of the patient to remove these products should be utilized as necessary.^{107 133 181}

The gas used for artificial respiration should always be 100 per cent oxygen except in carbon monoxide poisoning.^{205 208} It has been demonstrated that with the addition of 5 to 10 per cent of carbon dioxide to the inhaled atmosphere, the elimination of carbon monoxide will be faster and the availability of oxygen to the tissues will be increased.^{107 209 211}

The second aim of resuscitation in asphyxial accidents—that of providing support to the failing circulation—includes measures to combat shock and stimulate heart function.²¹²⁻²¹⁴

If facilities permit, fluid therapy should be administered intravenously, and measures by which the venous return to the heart can be increased, such as the Trendelenburg position, raising the legs to the vertical position ("autogenous transfusion") and application of tourniquet to the extremities, should be utilized.^{215 219} Normal body temperature should be maintained, but care must be taken not to overheat the patient.²²⁰

Employment of drugs that stimulate circulation such as epinephrine, ephedrine and related amines should be resorted to only if complete oxygenation has been established.^{215, 218 221}

During the aftercare when the patient has regained spontaneous respiration, further inhalation

and fluid therapy, supervision of a free respiratory exchange, attention to bladder and bowel functions and the maintenance of body temperature are in the realm of general nursing care but are essential components of thorough treatment

* * *

A trend that had developed over the past twenty years has led to an undesirable situation regarding asphyxial accidents. This situation is characterized by overzealous activities of lay rescue squads and at the same time a lack of professional interest in problems of resuscitation on the part of the physician. Insufficient essential knowledge of the anatomy of the respiratory tract, physiology of respiration, pneumatology, physiology of anoxia, pathological physiology and diagnosis of asphyxia is an obvious limitation to the capabilities of the lay rescuer. That this limitation is often not appreciated is evidenced by the calls to lay rescue squads that originate even from the operating and delivery rooms. The attitude of the medical profession frequently implies that the treatment proffered by the mechanical performance of the lay squad, aided by the inhalator, leaves nothing more to be desired.¹³³

The resolution by the American Medical Association to encourage instruction of medical students and postgraduates in pneumatology and in the treatment of asphyxial accidents, the activities of the Society for the Prevention of Asphyxial Deaths, Incorporated, and the inclusion of resuscitation as a basic subject in the specialty of anesthesiology, along with other efforts on the part of the medical profession, are laudable measures for the improvement of the situation.^{222 223} It is hoped that in the future, in the words of Flagg¹³³ "When the average physician looking upon impending asphyxial death is shocked into a realization that here and now is the supreme test of his life-saving skill as a physician, resuscitation will cease to be relegated to the care of those lay groups whose services have been and continue to be a bridge to span the period between helplessness and adequate medical care."

We gratefully acknowledge the co-operation of the residents and interns of the Anesthesia Department of the Boston City Hospital.

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stopped drinking and "has not touched a drop since."

Physical examination revealed an acutely ill, well developed, well nourished moderately pale man. The skin was hot and dry. There was a single "spidery angioma" on the left upper arm. A dilated venule that "seemed to end abruptly" was found on the posterior pharynx. The chest was clear. The heart was slightly enlarged to the left. The rhythm was regular, and the sounds were hyperactive. A Grade II systolic murmur was heard over the entire precordium and was transmitted to the axillas and neck. The abdomen was nontender and not distended. The liver edge was barely palpable at the liver margin. The spleen was not felt. Peristalsis was diminished. Rectal examination was negative.

The temperature was 102.6°F, the pulse 130 and the respirations 30. The blood pressure was 80 systolic, 50 diastolic.

The hemoglobin ranged from 11 to 12.5 gm. The white-cell count was 17,000, with 78 per cent neutrophils. The platelets were normal morphologically. There was slight erythrocytic hypochromia. The urine specific gravity was 1.025. The sugar test was brown, but intravenous glucose solution was being administered. A stool was brown and gave a + guaiac reaction.

Throughout his short hospital course the patient remained acutely ill, constantly febrile and in a constant state of shock. At intervals of one to four hours he vomited copious quantities of bright-red blood, losing a total of 4500 cc. by hematemeses. Parenteral injection of vitamin K and 6000 cc. of blood were administered during the first twenty-four hours. Attempts at esophageal tamponade were unsuccessful because of vomiting. Large doses of sedatives were given, and a state of semidelirium developed. At the end of twenty-four hours his condition stabilized somewhat. The blood pressure rose to 140 systolic, 70 diastolic, but tachycardia persisted. An emergency barium study of the esophagus was reported as showing "unequivocal varices." Twelve hours later there was a sudden drop in blood pressure to 80 systolic, 60 diastolic. Respiratory and cardiac failure quickly ensued despite the rapid administration of 1000 cc. of blood.

Large amounts of blood welled into the pharynx, and the patient died thirty-six hours after entering the hospital.

DIFFERENTIAL DIAGNOSIS

DR MILES P. BAKER: This is a brief story of massive hematemeses in a forty-eight-year-old man who was brought to the hospital bleeding to death, with a history of a similar but less severe hematemeses five months before, unexplained as to etiology.

The problem facing his physicians, primarily, was to save his life. That involved certain diag-

nostic procedures, because they had to consider the possibility of bleeding peptic ulcer for which surgical treatment might be necessary—hence, I suppose, the so-called emergency barium study of the esophagus done during the twenty-four hours preceding death. Was that only a fluoroscopic observation, Dr Mallory?

DR TRACY B. MALLORY: I cannot be sure.

DR BAKER: The data regarding the first hematemeses were, I suppose, obtained from the family. I think that one of the critical findings during that first episode of hematemeses was the jaundice. It is noted in the protocol as developing promptly after transfusions, which led to reactions. Reactions following transfusion are generally reported as occurring in approximately 6 per cent of cases, even when all reasonable precautions are taken. Reactions are not usually hemolytic—usually mild, febrile or urticarial. It is well to remember that chill following transfusion does not necessarily mean that hemolysis has taken place. The rule, as far as jaundice is concerned following transfusion, is that it can be expected about twelve hours after transfusion if a hemolytic reaction has taken place, it is a transient affair and is no longer observed after the passage of three or four days, at the most. My impression, then, of this comment that jaundice promptly developed is that jaundice was observed at that time but may have been present for some time before. Often, people recognize jaundice at a given time, but actually it has been there quite a while. Jaundice that took two weeks to fade, I would think, was much more likely due to liver disease. It would be consistent with an episode of jaundice in the course of cirrhosis of the liver. Jaundice in cirrhosis of the liver is statistically common, but it has to be remembered that it is of ominous prognostic significance. Once it appears, it generally does not disappear entirely, as the jaundice appears to have done in this man over his convalescent period of three or four months between hematemeses. I should say that the chances of having jaundice with cirrhosis of the liver, as a result of functional disturbances of the liver cells, and having it disappear would be no more than one chance in five or six—so that my stand that this jaundice was due to liver disease rather than any hemolytic reaction is something of a far cry. But I would prefer it to explaining the jaundice on the basis of hemolytic reaction to blood transfusion.

We have no evidence of any chemical studies to support either explanation for his jaundice. The prothrombin time of 75 per cent of normal is barely below what is found in a good many people when prothrombin times are determined on the wards. Of course, it must be below 20 per cent of normal before one runs into any serious hemorrhagic trouble, and this one finding is rather a weak reed for a diagnosis of cirrhosis of the liver. Could a prolonged prothrombin time be the one abnormal liver-function

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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CASE 35371

PRESENTATION OF CASE

A forty-eight-year-old truck driver was admitted to the hospital because of severe hematemesis

Five months before admission, while in a distant city, the patient suffered a sudden severe hematemesis. Several "liver-chemistry studies" performed at that time were normal, except the prothrombin time, which was 75 per cent of normal. The findings on a gastrointestinal series were somewhat equivocal but suggested esophageal varices, gastritis and "possible ulcer in the first portion of the

duodenum." He was given five transfusions, "the last four of which gave him reactions." Jaundice promptly developed, and the icteric index rose to 18 units. Administration of vitamin K failed to improve the prothrombin time. Bleeding stopped, and over the ensuing two weeks the jaundice faded. He lost 15 pounds in weight during the illness, and spent the following three months in convalescence before returning to his truck route. During the convalescent period an additional transfusion was administered to the patient without event. Eight teeth were extracted, after which blood oozed from the gums for what was considered a prolonged period. The gastrointestinal series was repeated, but no abnormalities were discovered. He returned to work and felt well, remaining free of symptoms until the day of admission. While driving his truck he "felt sick" and then suddenly vomited a large amount of blood. During the five hours required to transport him to the hospital, he had five additional episodes of vomiting. He felt weak, nauseated and intensely thirsty but not faint or "sweaty." Since the onset he had had one brown bowel movement.

His mother had died of cancer. His wife had suffered from tuberculosis at the time of their marriage, twenty years before admission, but had been in good health at the time of her husband's illness.

As a young man the patient had drunk large quantities of beer, up to several quarts a day. In recent years he had reduced the intake to a bottle a day. Six months before entry he spontaneously

I would like to vindicate the outside x-ray findings. This man had large and definite esophageal and gastric varices and also a very severe gastritis, which was hemorrhagic in part. There was a deep crater-like lesion of the duodenum that looked at first glance like a deep penetrating ulcer. In its center was a ridge that proved to be the common bile duct. It was lined by normal mucous membrane and represented a congenital diverticulum. The ampulla of Vater is a common site for such a lesion. On x-ray examination it could readily be interpreted as an ulcer crater. The stomach showed on microscopical examination a severe gastritis associated with the presence of a great many bacteria on the surface—a rather unusual finding in the stomach, since most stomachs are sufficiently acid so that organisms do not grow.

DR ALFRED KRANES: Were you able to demonstrate varices?

DR MALLORY: They were very marked and abundant, and I think they were the primary cause of hemorrhage, although the lesion in the stomach must have bled to some degree as well.

A PHYSICIAN: Was the spleen enlarged?

DR MALLORY: Only slightly. He had bled enormous quantities. The spleen, at autopsy, following hematemesis, is frequently considerably smaller than it has been during life.

Microscopical examination of the liver showed something that I believe casts light upon the transient episode of jaundice five months before the terminal events. There were many small foci of fresh, infarct-like necrosis irregularly scattered throughout the organs. Usually, they were about 1 mm in diameter and involved part or all of a small nodule of regenerated liver cells. This is not an infrequent finding in cirrhosis when severe hematemesis has preceded death by a number of hours. My explanation is that the blood supply in these scarred, irregularly reconstructed organs is no longer uniform. When hemorrhage from varices lowers the portal pressure and shock lowers the arterial pressure, ischemic damage occurs at susceptible points and liver function may be significantly depressed. It is not rare to see transient ascites develop following hematemesis, and jaundice, though less usual, would develop by the same mechanism and disappear when the liver circulation once again improved.

CASE 35372

PRESENTATION OF CASE

A two-day-old baby girl entered the emergency ward in an oxygenated incubator with pronounced abdominal distention and vomiting.

This was the mother's first pregnancy and was without incident. Delivery, at an outside hospital, proceeded normally, prophylactic low forceps being

used, breathing was spontaneous, and the cry was vigorous. The infant remained active and apparently well for the first twenty-four hours. On the second day of life, her color was described as "dusky," and she vomited dark, bloody fluid with her first feeding. Each subsequent feeding elicited vomiting. A small amount of meconium was said to have been passed by rectum on one occasion only. An enema produced only a small amount of meconium in addition to a 2-cm plug of mucoid material. On the next morning she was considered normal by an examining pediatrician. Late that afternoon, "caput medusae" of the abdomen, distention and cyanosis were noted. The baby continued to vomit feedings and became progressively cyanotic and more distended. She entered this hospital fifty-six hours after birth.

Physical examination revealed a very ill infant, with cyanosis, which was more evident over the lower half of the body. Respiration was shallow and rapid, coarse, squeaky rales were present throughout both lung fields, more intense on the right. No cardiac murmur was noted. The abdomen was greatly distended without auscultable peristaltic sounds. No meconium was obtained on rectal examination. The anterior fontanel did not bulge.

The temperature was 98.2°F.

The white-cell count was 8200. The eosinophilic count was 0 per cent.

Radiograms in the supine position revealed marked upward displacement of both leaves of the diaphragm and compression of the lung fields by a distended abdomen. There was gaseous distention of the stomach and several loops of small bowel. In the right lower quadrant there was a C-shaped loop of dilated gas-filled bowel, possibly small bowel, measuring 2.5 cm in diameter. Throughout the abdomen there was a diffuse haziness indicative of intra-abdominal fluid.

A stomach tube was passed, and greenish substance obtained. A rectal tube was inserted. Infusions, chemotherapy and supportive measures were instituted.

Further radiograms in both the supine and upright positions revealed, in addition to the previous findings, a decompressed stomach and a large quantity of free gas and fluid in the peritoneal space (Fig 1).

With continuous oxygen administration, abdominal paracentesis was done. One hundred and five cubic centimeters of dark brownish fluid with specks of yellowish-white material was obtained. Smears of this revealed copious gram-negative rods and gram-positive diplococci. Cyanosis increased. Respiration became irregular with periods of apnea. Artificial respiration was begun. Epinephrine, 0.5 cc, was given intracardially. Despite continued artificial respiration, cyanosis deepened and the infant died five hours after admission.

test in cirrhosis of the liver? Yes, it could be, but it is uncommon

The significance of the bleeding from the gums during the period of convalescence is, I think, very dubious. We cannot lay any stress on it. At the time of his first and final admission here one single spider angioma was observed on the left upper abdomen. This may or may not have been of really diagnostic importance. Spider angiomas are found in varying percentages of patients reported with cirrhosis, depending on the interest of the observer and the carefulness of the examination. They have been reported by careful observers in 75 per cent of a series of proved cases of portal cirrhosis. I can recall a case presented here this spring in which a single spider angioma observed by a visiting physician — and not previously recognized as such by others — was associated with proved fatty changes in the liver. In that case it was a very important diagnostic point. Spider angiomas do occur in other diseases — in vitamin B complex deficiency, notably. But the genuine article is usually associated with hepatic disease, and that is usually portal cirrhosis. I am surprised at the height of the hemoglobin figure, and cannot explain it in a patient who was in shock. I suppose it was taken at the time when he had just had a transfusion and had not yet begun to bleed again. I presume, with the roentgenologic observation, that there were unequivocal esophageal varices, that the medical officers in charge of the case expected that at post-mortem examination cirrhosis of the liver would be found. Is it possible to have such an advanced stage of cirrhosis of the liver that esophageal varices are present and detectable by x-ray study and bleed, with normal liver-function tests? It must be the exception to the rule. One roentgenologist who has had a great deal of experience with the demonstration of esophageal varices tells me that although he could not put his finger on an individual case he believes that they must occasionally occur. We do not know what liver-function studies were done five months before admission, and no attempt could be made at this admission for further studies, but it would surely not be unreasonable to assume that bleeding esophageal varices were the cause of this man's death.

What other possibilities might there be? Peptic ulcer is the commonest cause of massive hemorrhage in the upper gastrointestinal tract, accounting for probably 60 to 75 per cent of such cases. We must consider it in any event — if only on the basis that the x-ray examination five months before suggested an acute duodenal ulcer. The association of cirrhosis of the liver and duodenal ulcer has been commented on several times, whether it is more than a coincidence or not is not established. So, even if this man did have unequivocal evidence of esophageal varices just prior to death he still may have

been bleeding fatally from a duodenal ulcer. Such an explanation has been advanced under similar circumstances in cases presented here. If this man had cirrhosis of the liver, he may have been bleeding, if not from esophageal varices, from a much engorged mucous membrane in the upper third of the stomach, sometimes found in such cases either in association with, or in the absence of, erosions of varices in the lower end of the esophagus.

It is noted here that the hematemesis was described as "copious quantities of bright-red blood." That might be interpreted as arterial blood, more typical, perhaps, of the bleeding from duodenal ulcer or gastric ulcer than from esophageal varices. On the other hand, it is so characteristic for the patient with bleeding esophageal varices to have blood well up into the pharynx that there may be evidence here on one side as well as the other.

My impression is that this man had cirrhosis of the liver and bleeding esophageal varices. There may have been an associated duodenal ulcer, which was a primary factor in his bleeding, but we have no more than a suspicion for it.

A PHYSICIAN Did he have an enlarged spleen?

DR. BAKER Not enlarged, so I should think one had no reason to consider congestive splenomegaly — Banti's disease.

CLINICAL DIAGNOSIS

Ruptured esophageal varices
Laennec's cirrhosis?

DR. BAKER'S DIAGNOSES

Portal cirrhosis
Esophageal varices, with massive and fatal hematemesis
Duodenal ulcer?

ANATOMICAL DIAGNOSES

Portal cirrhosis of liver, alcoholic type
Esophageal and gastric varices, with ulceration and hemorrhage into gastrointestinal tract
Gastritis, acute
Diverticulum, congenital, of duodenum

PATHOLOGICAL DISCUSSION

DR. MALLORY Autopsy on this man showed a cirrhotic liver. It was enlarged, very finely granular, tough, pale and evidently fatty. Its gross appearance and the subsequent microscopical findings were characteristic of what we ordinarily call alcoholic cirrhosis of the liver, despite the history of the consumption of nothing stronger than beer, and not even that for the last six months. One can interpret that as one chooses. The man was a truck driver, and a written record of alcoholism might have caused him to lose his job so I do not believe one can take it at its face value. Moreover, truck drivers as a group eat very well, so that malnutrition is very unlikely unless provoked by alcoholism.

Thrombophlebitis of the portal system can lead to gangrene of the bowel and subsequent rupture. I doubt whether such a process could take place in so short a time as the history indicates. Cyanosis, more evident in the lower extremities, suggests involvement possibly of the vena cava and iliac veins, most likely by compression. The absence of peristalsis suggests peritonitis and ileus.

Before going on to the x-ray studies, I believe we should say a word or two about the meconium. As one notes, very little was passed. The mucoid plug is a normal finding—often referred to as a “meconium plug.” In the normal infant this is usually followed by the characteristic tarry, sticky meconium. After the plug was passed no further meconium was reported. Rectal examination failed to reveal any. This suggests obstruction from either atresia or inspissated meconium. A helpful test for atresia is the absence of cornified cells in the meconium. These cells from the vernix caseosa are desquamated into the amniotic fluid, which is swallowed by the fetus in utero. If no atresia exists, their presence can be detected in the meconium.

May we see the x-ray films?

DR STANLEY M. WYMAN: In the first film, which is of rather poor quality, the stomach is distended and the gas in the abdomen obscures the liver shadow, with a C-shaped loop of dilated bowel in the right lower quadrant. The diaphragm, as recorded, is displaced upward, and the lung fields are slightly compressed. A short time later, after the stomach had been aspirated, the gas in the stomach is decreased to normal, but the C-shaped loop of bowel in the left midabdomen remains. Again, gas is seen obscuring the shadows of the liver and spleen. This next film was taken at the same time in the upright position and shows a large quantity of gas with fluid in the abdomen. I do not see any evidence of gas in the colon.

DR BURGIN: Have you any idea where the C-shaped loop would be?

DR WYMAN: I should say that it was the ileum.

DR BURGIN: The haziness reported in the first set of films as fluid need not indicate peritonitis. In infants, distention of the intestines alone may cause fluid to accumulate. Subsequently, there was evidence of rupture of a hollow viscus—obviously bowel—and the presence of the usual flora in the newborn: colon bacilli and, I presume, enterococci.

I believe the evidence points to intestinal obstruction due to an intrinsic lesion relatively low down in the bowel, which eventually resulted in rupture. The intestinal wall of the newborn is extremely thin, and rupture occurs relatively quickly if the distention is not relieved. I consider atresia the most likely cause of the lesion, although inspissated meconium—“meconium ileus”—remains an outside possibility.

In summary, early persistent vomiting, increasing generalized abdominal distention, absence of stools, accumulation of fluid and finally x-ray evidence of gas in the peritoneal cavity and distention of stomach and loops of bowel point to a diagnosis of atresia of the small bowel with rupture. On the basis of statistical frequency the atresia was most likely in the ileum. There should have been evidence of rupture, peritonitis, atelectasis and possibly some pneumonia.

DR F. DENNETTE ADAMS: In babies would there be distention enough to cause cyanosis?

DR BURGIN: Certainly the newborn can become distressed following a meal causing difficulty in breathing. Mothers report that, after eating, a baby may have difficulty in breathing due to a distended stomach but not enough to produce cyanosis. I passed over the possibility of stenosis; there may be a patency of only 1 or 2 mm in diameter, and for all practical purposes this may give signs and symptoms of obstruction.

CLINICAL DIAGNOSES

Congenital atresia of small bowel
Peritonitis due to perforated viscus

DR BURGIN'S DIAGNOSES

Congenital atresia of the bowel (ileum), with rupture
Colon-bacillus peritonitis
Pulmonary atelectasis
Pneumonia?

ANATOMICAL DIAGNOSES

Congenital defect of mesentery, with volvulus and perforation of ileum
Peritonitis
Pulmonary atelectasis, severe

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: At autopsy when the abdomen was incised large amounts of hemorrhagic fluid exudate were found. The entire small bowel was dilated, the dilatation increasing as one progressed downward from the duodenum. The cause of this was discovered as the lower ileum was reached. A congenital defect was found in the mesentery through which a loop of ileum had protruded and then twisted on itself, forming a volvulus. Evidently at a later period three small perforations had developed in the gangrenous bowel of the volvulus.

Regarding the cyanosis, the astonishing thing at autopsy was that the child had breathed at all. The lungs were as totally atelectatic as those of a newborn baby who has never taken a breath. It was difficult to understand how the child could have lived long enough to develop such persistent and complete collapse.

DIFFERENTIAL DIAGNOSIS

DR. LEO B. BURGIN In brief, we are faced with the problem of determining the cause of a series of events following one another rapidly in a two-day-old infant: persistent vomiting, abdominal distention, cyanosis, paralytic ileus, intra-abdominal fluid



FIGURE 1

and terminally gas and probably pus in the peritoneal space, with death at sixty-one hours.

A number of possibilities present themselves, in particular, congenital malformations of the gastrointestinal tract, meconium ileus and infection. Other possibilities may come to mind as the discussion proceeds.

Vomiting as a single episode or with occasional repetition is not uncommon in the normal newborn. The first episode described "dark bloody fluid." This may have had no further significance than that it represented aspiration of the blood at the time of delivery. There was no repetition of this

It was early for hemorrhagic disease of the newborn. Subsequently, the infant vomited at each feeding. We are not told the nature of the vomiting, whether it was projectile or merely regurgitation. Also, no description of the vomitus is offered. Later, "greenish" material was aspirated from the stomach, suggesting the presence of bile. An obstructive lesion under such circumstances would exist below the ampulla of Vater. Such an obstruction might be in the nature of atresia or stenosis, inspissated meconium or possibly malrotation of the cecum—the unrotated cecum lying across the lower end of the duodenum.

Vomiting is a frequent occurrence in infection. Although infection existed terminally as peritonitis, there was nothing to indicate its presence earlier. The white-cell count and temperature on admission were normal. Overwhelming infection or sepsis in the newborn may be present with a normal temperature and white-cell count. The eosinophilic count of 0 per cent merely indicates adrenal response or perhaps more accurately the "alarm-reaction" response to an overwhelming insult to the body. The absence of a bulging fontanel rules out intracranial vomiting, though not absolutely.

The rales in the chest might indicate pneumonia, but very likely some atelectasis and compression from a distended abdomen were largely responsible. One cannot rule out pneumonia.

The persistent vomiting was followed by abdominal distention, which appears to have been generalized. Obstruction in the region of the duodenum is apt to cause distention in the region of the epigastrium. Peristaltic waves are often visible. None were reported here.

It appears that in this case, the distention being generalized, any obstruction must have been lower down. This might rule out a malrotated cecum, which commonly lies across the third part of the duodenum. I might point out that in this anomaly the mesentery of the small bowel may lack the normal fixation, so that volvulus of the midgut, with gangrene and necrosis, may occur and might conceivably give the picture described. As we have indicated, distention caused by the unrotated cecum would be localized to the epigastrium—at least in the beginning. I assume that the generalized distention recorded here appeared almost at once. Also, the obstruction would not have been complete in the beginning, and we would have evidence of more stools or meconium to indicate patency of the gut.

The sudden appearance of a "caput medusae" suggests involvement of the portal vein, either from compression by distended gut or possibly from thrombophlebitis. The source of infection might be via the umbilicus, although the record says nothing about its appearance. It could look normal at this time and still be the source of infection.

parts of the country and had kept in a frozen state. They were unable to isolate the virus from two pools of feces, one obtained in New York in 1944 and the other in Los Angeles in 1948, both these pools yielded poliomyelitis virus on inoculation of monkeys. They did, however, recover both the new virus and the poliomyelitis virus from a pooled specimen of feces from 6 patients with nonparalytic poliomyelitis in Akron, Ohio, in 1947, and from another pooled specimen collected in Winston-Salem, North Carolina, in 1948. In addition, they were able to isolate the virus from the sewage of 6 cities in areas where the virus had been isolated from patients. Furthermore, the new agent was isolated from flies trapped in at least two of the same areas. A number of batches of flies collected during the epidemic of poliomyelitis that occurred in Texas in 1948 were also studied. Some of these yielded the new virus alone, others yielded only the poliomyelitis virus, and still others yielded both viruses.

The findings of the Yale workers indicate that the virus of Dalldorf and Sickles was widespread in this country in 1948 and possibly also in 1947. It is not yet entirely clear whether this is really a new virus that has made its first appearance as a human pathogen during recent years or whether it has been a factor in earlier outbreaks of paralytic infections in this country and elsewhere. The answer to this and to many other epidemiologic questions should be forthcoming as more of the stores of materials collected by these and many other workers on poliomyelitis are restudied. Further investigation should also indicate whether the epidemiology of the disease caused by the new virus is the same as that of poliomyelitis or whether it differs in such factors as seasonal distribution and the types of persons affected. The findings to date suggest that both viruses have similar epidemiologic features.

Although all the patients from whom the Yale workers isolated the strains of the new virus had nonparalytic cases, the original observations of Dalldorf and Sickles suggest that the disease caused by the new agent is not innocuous. Both their patients had definite muscular paralysis, and in one on them some of the paralysis was still present after

seven months. It is also not yet clear how often this new virus will be discovered in clinical cases with paralysis. It is evident that the new virus has been found in areas and during periods in which paralytic poliomyelitis has been prevalent, but it remains to be seen how often it will be isolated in areas free of poliomyelitis and at times when this virus is not usually to be expected. The full clinical implications of these findings are therefore not yet evident. It is already apparent, however, that the diagnosis of poliomyelitis even during epidemics has now become further complicated in that infections with this new virus will have to be considered both in paralytic and in nonparalytic infections.

The spinal fluid in 9 out of 11 patients in whom infections with the new virus was demonstrated in New Haven showed a pleocytosis. The total number of leukocytes ranged from 27 to 600 per cubic millimeter, with 27 to 95 per cent mononuclear cells. There was a patient, however, from whom the virus was isolated and whose spinal fluid showed only 3 cells. Further correlations of both clinical and laboratory findings in patients with proved infections with this new agent and with the poliomyelitis virus are also needed to determine to what extent the two diseases, in both the paralytic and the nonparalytic forms, can be distinguished on the basis of simple clinical and laboratory findings. The recent observations indicate that, like the poliomyelitis virus, the new agent may produce fever without any specific meningeal or muscular symptoms. Infections with the new virus must therefore be included in the differential diagnosis of acute cases of "fever of unknown origin."

At the present time the demonstration of infections with the new virus of Dalldorf and Sickles is still a task for the few laboratories engaged in virus research. It is hoped that with further developments, less elaborate methods may be worked out that could be more readily applied in the usual hospital bacteriologic and serologic laboratories.

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NEW VIRUS FROM DISEASES RESEMBLING POLIOMYELITIS

EARLY last summer Dalldorf and Sickles,¹ of the Division of Laboratories and Research of the New York State Department of Health in Albany, reported the isolation of a filtrable agent from the feces of 2 patients with muscular paralysis. These cases were observed during a small outbreak of poliomyelitis in upstate New York in August, 1947. The virus was distinct from that of poliomyelitis in that it could be isolated only by intracerebral inoculation of suckling mice or hamsters, but monkeys were not susceptible. The lesions produced consisted of widespread degeneration of the skeletal muscles, without any apparent lesions in the central nervous system or the large peripheral nerves.

The properties of this agent were different from those of any other known viruses. Furthermore,

since it was recovered from patients with paralysis during a time when poliomyelitis was occurring to some extent in several areas of the country, it became a matter of considerable importance to learn more about its prevalence and its relation to clinical poliomyelitis. These workers, therefore, published their preliminary observations with the hope that other investigators would search for this agent and that some of them might perhaps have an opportunity to study the muscles in fatal cases of paralytic disease.

The first confirmation and extension of the findings of Dalldorf and Sickles has recently been published by Melnick, Shaw and Curnen,² of Yale University School of Medicine. The New Haven workers obtained a virus from the feces of 5 out of 13 patients with illnesses that resembled those of nonparalytic poliomyelitis or the so-called aseptic meningitis and from 2 additional patients with diagnoses of "fever of unknown origin." All their cases occurred in Connecticut and in Rhode Island during the summer and fall of 1948. They were also able to demonstrate neutralizing antibodies in the convalescent serums of all the 7 patients from whose feces the virus was isolated and in 5 additional patients with nonparalytic illness in whom attempts to isolate a virus were unsuccessful.

The properties of the virus obtained by the New Haven workers were the same as those of the agent isolated in Albany. The Yale workers were also able to demonstrate inapparent infection in chimpanzees after oral administration of the virus by recovering the virus from the nasopharynx and feces of these animals and also by proving the development of neutralizing antibodies for the new agent. In addition, one of the New Haven workers developed an accidental infection, which was characterized by fever of eight days' duration and a minimum of stiffness of the back, but no definite central-nervous-system symptoms. The new virus was recovered from the nasopharynx and feces of this worker, and neutralizing antibodies for the agent developed in his serum in increasing titer during convalescence.

Melnick and his associates extended their observations by a study of samples of feces that they had collected in previous outbreaks in different

in particular the conditioned-reflex treatment of chronic alcohol addiction as it is carried out at the Washingtonian Hospital in Boston

The conditioned-reflex treatment, at present the most promising form of therapy for alcoholism, was first reported in England in 1930. Apomorphine was the drug used in these early experiences, and an estimated success of 35 per cent was attained. In this country the Shadel Sanitarium in Seattle, Washington, first reported nearly a decade ago a considerable number of patients treated with the conditioned reflex. A 78 per cent solution of emetine was used, and 64.3 per cent total abstinence was claimed as a result. A further report from this institution was published a year ago in the *Journal*¹

At the Washingtonian Hospital, where the conditioned reflex was instituted seven years ago, a slightly modified technic has been adopted, supplemented by "methodic psychotherapy and part-time hospitalization and manipulation of the patient's environment."

Emetine is a drug not without its disadvantages, as is indicated by Thimann and has been pointed out by Kattwinkel² in his report of a case treated with emetine, with a fatal outcome. It lowers the blood pressure and in excessive doses causes arrest of the heart in diastole. The nausea induced by it may be accompanied by diarrhea, and it may be followed by muscular pain and weakness.

In its effects on the cardiovascular system lie the chief objections to emetine, Thimann reporting that 5 of the 282 patients in his series had cardiovascular manifestations, with 2 deaths. The death reported in detail occurred in a patient who flagrantly disregarded instructions.

The precautions that should be taken to prevent untoward reactions are listed by Thimann and have been referred to editorially in these columns.³ If due consideration is given to them, emetine may be employed with safety, although the search for a less toxic substitute continues.

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BOSTON'S CHEST X-RAY PROGRAM

Boston, following the precedent established by various other large cities of the country, is about to launch an intensive chest x-ray program. The campaign will start on September 21 and continue until January 14; its goal is to obtain a chest x-ray examination, if possible, of every person of fifteen years of age or over who lives, works or transacts business in the city.

The younger age group is excluded from the program because of its much lower incidence of tuberculosis and because of other screening methods that are more effective than mass x-ray study—such as tuberculin testing, and case finding as a result of the adult program.

The program will be conducted under the auspices of the Boston Health Foundation, Incorporated, an organization made up of the vital health and welfare agencies of the city, which have united at this time for this specific purpose. A far-reaching system of committees has been devised, each with its particular area of responsibility. Not the least important among them is the medical committee, under the chairmanship of Dr. Dwight O'Hara, which is further divided into subcommittees for the interpretation of the program to physicians, for the supervision of and the proper referral of positive cases, and for the review of those cases that require it.

Suitable personnel and twenty mobile x-ray units are being loaned by the United States Public Health Service for the program, and these will operate, area by area, in twenty health districts established as such for the occasion. Persons with normal chest x-ray films will be promptly notified of the fact by mail, those showing any suspicion of active tuberculosis, cardiovascular disease or other pathologic conditions will be referred to their physicians, and their physicians will be so notified.

Boston, with a tuberculosis death rate in 1948 of 56.1 per 100,000 population labors under the distinction of a rate nearly twice that of the country as a whole. The program that is about to start will be of great value in correcting this situation. Of the greatest value in furthering the enterprise will be the co-operation of the medical profession in the best New England tradition of service.

"REVERENCE FOR LIFE"

AMERICA has entertained briefly on his first visit to its shores one of the world's foremost if hitherto little known physicians. Albert Schweitzer, now nearly seventy-five years of age, the son of an evangelical pastor of Alsace, has excelled in a half dozen of life's pursuits where it is given to most men to participate in only one or two.

A preacher, writer, teacher, philosopher and musician, the world's greatest interpreter of Bach, Schweitzer, when the time came, turned his back, upon the exploitation of these accomplishments, renounced the material rewards of his genius and became a medical missionary in Equatorial Africa.

Schweitzer's character, so far as it is readily definable, is revealed in the titles of his works. *The Religious Philosophy of Kant* was published when he was 24, three years after he had determined that he would consider himself justified in living until he was 30 for science and art, "in order to devote myself from that time forward to the direct service of humanity." In 1903 he began *The Quest of the Historical Jesus*. His biography of Bach is the standard text on the life of that musician, but his autobiography, *Out of My Life and Thought* remains his best known work. *The Philosophy of Civilization* will be published this fall.

Like many who have attained their goal less completely, if no less humbly, Schweitzer came early to the conclusion that for him true happiness could be achieved only through a life of self-sacrificing service to others. To that goal he would channel his brilliant attainments, after he had brought them to maturity.

Still earlier he had adopted his own secret prayer to "protect and bless all things that have breath, guard them from all evil, and let them sleep in peace." He tells later in his autobiography, as quoted by Sperry* in these pages, how the definition of this belief finally came to him.

Journeying up the river toward his hospital he was searching in his mind for some basic ethical principle, but fruitlessly. And then

Late on the third day at the very moment we were making our way through a herd of hippo-

potamuses, there flashed upon my mind, un-foreseen and unsought, the phrase "Reverence for life." For all life

This was the essence of the belief that had moved him, at 21, to continue his brilliant career in music and in preaching for only ten years more and then to study medicine and give his life wholly to others. It was the credo that brought the ultimate happiness of contentment to his mind, previously troubled despite his intellectual achievements and material success, the abnegation that always must motivate the priest or the missionary whether in foreign fields or in areas of service nearer home.

This same reverence for life and willingness for sacrifice in its behalf provide the basic material in the character of the true physician wherever his course may lie.

It is of little moment whether Schweitzer's decision was partly intellectual or wholly emotional or whether the services that he has performed in darkest Africa, comparable to those of Grenfell in Labrador, might have reaped a more productive harvest in some more fruitful area. All life, according to his uncompromising standards, must be revered and consequently preserved and strengthened and upheld.

DEMON RUM

THE fact that the uncertainties of life in a complex world lend added attraction to the offerings of the neighborhood package store accounts largely for man's eager resort to alcoholic beverages. In peaceful times as well as in disturbed ones, however, in simple as in complicated surroundings, thinking man, so far the supreme product of nature's biologic efforts, still finds it necessary to bypass with the help of alcohol the results of his ability to reason.

Some persons are able to use alcohol in this way to a limited degree and remain in general control of their activities, others—and the number is increasing—become slaves to the habit that they have acquired. Whatever the original cause of their addiction and whether or not it still persists, the addiction has with them become in itself a disease that requires treatment.

The two articles by Thimann, published a week ago and in the present issue of the *Journal*, discuss

*Sperry, W. L. Moral problems in practice of medicine. *New Eng J Med* 239:985-990, 1948.

in particular the conditioned-reflex treatment of chronic alcohol addiction as it is carried out at the Washingtonian Hospital in Boston

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At the Washingtonian Hospital, where the conditioned reflex was instituted seven years ago, a slightly modified technic has been adopted, supplemented by "methodic psychotherapy and part-time hospitalization and manipulation of the patient's environment."

Emetine is a drug not without its disadvantages, as is indicated by Thimann and has been pointed out by Kattwinkel² in his report of a case treated with emetine, with a fatal outcome. It lowers the blood pressure and in excessive doses causes arrest of the heart in diastole. The nausea induced by it may be accompanied by diarrhea, and it may be followed by muscular pain and weakness.

In its effects on the cardiovascular system lie the chief objections to emetine, Thimann reporting that 5 of the 282 patients in his series had cardiovascular manifestations, with 2 deaths. The death reported in detail occurred in a patient who flagrantly disregarded instructions.

The precautions that should be taken to prevent untoward reactions are listed by Thimann and have been referred to editorially in these columns.³ If due consideration is given to them, emetine may be employed with safety, although the search for a less toxic substitute continues.

BOSTON'S CHEST X-RAY PROGRAM

Boston, following the precedent established by various other large cities of the country, is about to launch an intensive chest x-ray program. The campaign will start on September 21 and continue until January 14, its goal is to obtain a chest x-ray examination, if possible, of every person of fifteen years of age or over who lives, works or transacts business in the city.

The younger age group is excluded from the program because of its much lower incidence of tuberculosis and because of other screening methods that are more effective than mass x-ray study—such as tuberculin testing, and case finding as a result of the adult program.

The program will be conducted under the auspices of the Boston Health Foundation, Incorporated, an organization made up of the vital health and welfare agencies of the city, which have united at this time for this specific purpose. A far-reaching system of committees has been devised, each with its particular area of responsibility. Not the least important among them is the medical committee, under the chairmanship of Dr. Dwight O'Hara, which is further divided into subcommittees for the interpretation of the program to physicians, for the supervision of and the proper referral of positive cases, and for the review of those cases that require it.

Suitable personnel and twenty mobile x-ray units are being loaned by the United States Public Health Service for the program, and these will operate, area by area, in twenty health districts established as such for the occasion. Persons with normal chest x-ray films will be promptly notified of the fact by mail, those showing any suspicion of active tuberculosis, cardiovascular disease or other pathologic conditions will be referred to their physicians, and their physicians will be so notified.

Boston, with a tuberculosis death rate in 1948 of 56.1 per 100,000 population labors under the distinction of a rate nearly twice that of the country as a whole. The program that is about to start will be of great value in correcting this situation. Of the greatest value in furthering the enterprise will be the co-operation of the medical profession in the best New England tradition of service.

REFERENCES

1. O'Holla, P. and Lemere, F. Conditioned reflex treatment of chronic alcoholism. *New Eng J Med* 239:351-352, 1948.
2. Kattwinkel, E. E. Death due to cardiac disease following use of emetine hydrochloride in conditioned reflex treatment of chronic alcoholism. *New Eng J Med* 240:995-997, 1949.
3. Editorial. Emetine in alcoholism. *New Eng J Med* 240:1029, 1949.

Perseverance is a prominent element in western character. It is infused into the institutions of learning as well as in river navigation. The medical department of the University of St. Louis is strongly organized, and the system of medical education in it is creditable to Missouri.

Boston M & S J, September 12, 1849

MASSACHUSETTS MEDICAL SOCIETY



The fall meeting of the Council of the Society will be held at 10 30 a m, October 5, at the Boston Medical Library

H QUIMBY GALLUPE, M.D.
Secretary

DEATHS

BERNHARDT — Henry M Bernhardt, M.D., of Arlington, died on August 31. He was in his forty-first year.

Dr Bernhardt received his degree from Boston University School of Medicine in 1935. He was physician for the Massachusetts Institute of Technology and Phillips Academy, Andover, and was a member of the New England Ophthalmological Society.

His widow, a son, a brother and a sister survive.

SCUDDER — Charles L Scudder, M.D., of Brookline, died on August 19. He was in his ninetieth year.

Dr Scudder received his degree from Harvard Medical School in 1888. He was a consulting surgeon at the Massachusetts General Hospital and was a fellow of the American College of Surgeons and the American Surgical Association and a member of the Society of Clinical Surgery and the New England Surgical Society.

A son and a daughter survive.

WASHBURN — Frederic A Washburn, M.D., of Boston, died on August 20. He was in his eighty-first year.

Dr Washburn received his degree from Harvard Medical School in 1896. He was formerly superintendent of the Massachusetts General Hospital and founded the Baker Memorial Hospital. He was director of the Massachusetts Eye and Ear Infirmary from 1915 to 1934 and was appointed commissioner of institutions in Massachusetts in 1934. He was a fellow of the American Medical Association.

His widow survives.

WILDER — Ella A Wilder, M.D., of Middletown, Connecticut, died on July 20. She was in her fifty-third year.

Dr Wilder received her degree from Boston University School of Medicine in 1923. She was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

Her mother survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

LABORATORIES APPROVED FOR DIAGNOSTIC SEROLOGY

Since the completion of the tests for 1948-49, the following laboratories have been granted approval. Only laboratories approved by the Department of

Public Health for diagnostic serology may legally make the premarital and prenatal blood tests required by law. This is in addition to the Wassermann Laboratory of the Department, which is evaluated annually by the Public Health Service.

LOCATION	LABORATORY
Boston	Boston Dispensary Boston Health Department Commonwealth Clinical Laboratory Leary Laboratory Massachusetts Memorial Hospitals Brockton Health Department Stas Laboratories Clinton Hospital Union Hospital Fairview Hospital Hale Hospital Holyoke Hospital Providence Hospital Lowell General Hospital Farren Memorial Hospital Burt Clinical Laboratory St. Luke's Hospital Newton-Wellesley Hospital Pittsfield General Hospital St. Luke's Hospital Quincy City Hospital Salem Hospital Mercy Hospital State Infirmary Noble Hospital Worcester City Hospital Worcester Health Department St. Vincent Hospital
Brockton	
Brookline	
Clinton	
Fall River	
Great Barrington	
Haverhill	
Holyoke	
Lowell	
Montague City	
New Bedford	
Newton	
Pittsfield	
Quincy	
Salem	
Springfield	
Tewksbury	
Westfield	
Worcester	

CORRESPONDENCE

INCURABLE READER

To the Editor Noticing the review of Dr Ronchese's book on *Occupational Marks and Other Physical Signs*, I was reminded of our old friend Dr Maurice Richardson. He was constantly urging us to observe. I remember one day he was questioning an unknown patient and asked, "Are you a steam or gas fitter?" Astonishment showed on the man's face as it did on the faces of the students. Dr Richardson smiled and pointed to a faint tattooed scar on the man's nose, shaped like a new moon.

I think this is the fifty-fifth or fifty-sixth continuous year that I have had the *Journal* and perused it with pleasure and profit — an outstanding journal.

PHILIP C MEANS, M.D.

Chula Vista, California

SEMANTICS

To the Editor I have just read your editorial "Essentially Useless" in the July 14 issue of the *Journal*, in which you rightfully call attention to "uncritical use of the language." I should like to point out the consistent use of the word "regime" in indicating in your journal a program of therapy. I have also noted in another of your editorials ("Medical Practice in Great Britain" in the *Journal* of February 3) the use of "regimen" as a system of government. The following definitions are given in my *Funk and Wagnalls Desk Dictionary*.

Regime, n. System of government or administration, social system.

Regimen, n. 1. A systematized course of living, as to food, clothing, etc. 2. Government, control.

It seems from the above that "regimen" applies either to government or to therapy, but that "regime" should be limited to use in referring to government.

HERBERT N JACOBS, M.D.

San Francisco

Note: Webster's *International Dictionary* (1948) is less scrupulous in the definition of regime. 1. Mode or system of rule or management, character of government or of the social system. 2. Hydraulic. 3. Med. Regimen — Ed.

ACROMIOCLAVICULAR DISLOCATION

To the Editor A perusal of Dr Boardman Marsh Bosworth's paper, "Complete Acromioclavicular Dislocation," which appeared in the August 11 issue of the *Journal*, prompts the following observations

Complete dislocation at the acromioclavicular joint is not invariably associated with avulsion of the coracoid and trapezoid ligaments, or as Dr Bosworth calls them, the "coracoclavicular ligament." This statement is based on the work of Poirier and Rieffel, in their study entitled "Mécanisme des luxations sus-acromiales de la clavicule leur traitement par la suture assidue" (*Arch gén de méd* 1 396-422, 1891), and of Cadanot, in his article "The Treatment of Dislocations and Fractures of the Outer End of the Clavicle" (*Internat Clin* 27 145-169, 1917). It has recently been confirmed by Urst in a paper entitled "Complete Dislocation of the Acromioclavicular Joint" (*J Bone & Joint Surg* 28 813-837, 1946). I was associated with Dr Urst during a part of the time he was carrying out his studies on this subject and can confirm his conclusions. On the basis of numerous dissections of fresh material and observations at the operating table, Urst states "When these structures (the joint capsule and attachments of the trapezius and deltoid muscles) were severed, to simulate the tearing or stretching which occurs in them with dislocation, complete dislocation of the outer end of the clavicle was possible without injury to the coracoid or trapezoid ligaments. It is true that rupture of the coracoid and trapezoid ligaments allowed greater displacement of the clavicle, but the picture was altered quantitatively, not essentially."

Integrity of the clavicle or its associated joints is not essential for normal function of the shoulder. Fitchet, in an exhaustive study entitled "Cleidocranial Dysostosis Hereditary and familial" (*J Bone & Joint Surg* 11 838-866, 1929), found almost no evidence of impairment of function in his cases or those reported in the literature. Although it is true that in the presence of injury to the clavicle or dislocation of the acromioclavicular joint the shoulder "droops" downward and forward, there is also an upward component of force that has not generally been recognized. Gordon, in 1875, called attention to this in his book, *A Treatise on the Fractures of the Lower End of the Radius, on Fractures of the Clavicle, and on Reduction of the Recent Inward Dislocations of the Shoulder Joint* (London: J & A Churchill), and pointed out that in the absence of the strut of the clavicle the muscles of the shoulder girdle as a whole tend to force the shoulder toward the apex of the truncated cone of the thorax.

Complete dislocation of the acromioclavicular joint is not incompatible with excellent function. I recently had an opportunity of examining a professional football player, who is able to throw forward passes with great skill despite the fact that the distal end of his clavicle lies on the superior surface of his acromion even at rest. Two similar cases in college athletes have been seen in the past two years.

Motion between the clavicle and the coracoid process of the scapula is considerable and complex. This can easily be demonstrated by a simple experiment, which was repeated today and in which a healthy, twenty-eight-year-old man, who had never suffered an injury to his shoulder girdle, was placed upright facing an x-ray cassette and films were taken with the arm hanging at the side and held directly overhead. Between the former and the latter the coracoid process moved 1 inch toward the distal end of the clavicle and rotated upward an estimated 40°, and the clavicle itself rotated on its own axis upward and backward an estimated 90°.

Fixation or "suspension" between the coracoid process and the clavicle such as Dr Bosworth advocates severely must strain either the fixation apparatus or the bones involved. The effect of the fixation seems to be the same as fusion of the acromioclavicular joint, which Dr Bosworth very properly condemns. Even if care is taken to leave the proximal end of the screw loose, as Dr Bosworth recommends, limitation of motion between the coracoid and the clavicle must be marked.

A plea for conservative management of acromioclavicular joint injuries was made by Thorndike and Quigley in a paper "Injuries to the Acromioclavicular Joint. A plea for conservative treatment" (*Am J Surg* 55 250-261, 1942). The results of treatment of 138 acromioclavicular dislocations or separations of varying degree in athletes were reported. In none was operation found necessary. As Urst

pointed out, associated injury to the trapezius and deltoid muscles plays a large part in separation of the distal end of the clavicle from the acromion after an injury to the shoulder. As the integrity and tone of these injured muscles return, an apparently severe separation often changes to a trivial laxity of the joint that produces neither symptoms nor disability.

Surgery, when necessary, is usually indicated for cosmetic reasons, or for relief of pain, which may accompany the imperfect function of chronic partial dislocation. In either case simple removal of the outer end of the clavicle, as recommended by Gurd, in his report entitled "Surplus Parts of the Skeleton" (*Am J Surg* 74 705-720, 1947), has been satisfactory. For the rare patient whose livelihood depends on prompt restoration of appearance and function, a lashing operation, using strips of fascia lata, may be indicated.

T B QUIGLEY, M D

Boston, Massachusetts

Dr Quigley's letter was submitted to Dr Bosworth, who offers the following reply:

To the Editor I was delighted to read Dr Quigley's comments on my recent paper and feel complimented that he was inspired to make them. Thank you for granting me the opportunity to reply.

It may be that complete dislocation can occur without tearing of the coracoclavicular ligaments. I have not seen this happen.

I believe that whether or not integrity of the acromioclavicular joint is essential for normal function is a matter of opinion and depends upon one's definition of "normal."

I admit that complete acromioclavicular dislocation may not be incompatible with excellent function, but, if it occurs, it must be the exception rather than the rule.

Dr Quigley is correct in stating that motion between the clavicle and the coracoid process is complex. Whether or not it is "considerable" again depends upon definition of that word.

Dr Quigley writes that of 138 acromioclavicular dislocations reported by him in 1942 none required operation. I congratulate him! However, he does not indicate how many of these were complete dislocations. This is the very crux of the problem, since treatment and prognosis will vary according to whether the joint separation is *partial* or *complete*. Any discussion of the subject that fails clearly to distinguish between the two merely confuses the reader. May I point out that the paper in question was expressly limited to *complete* dislocations.

Whether or not the insertion of a screw in the manner I describe is called "fixation" or "suspension" is beside the point. It works.

BOARDMAN MARSH BOSWORTH, M D

Bronxville, New York

A QUESTION OF CONSISTENCY

To the Editor I am somewhat confused by an apparent basic inconsistency between your interesting editorial on the Danish program for criminal psychopaths in the July 7 issue of the *Journal* and your fine editorial comment in the July 14 issue concerning Dr Alexander's sobering revelations of medical atrocities under Hitler.

The former editorial endorses the policy of the Danish program and refers with apparent approval to castration as a condition of release of sex offenders, "just as numbers of the inmates of mental-deficiency institutions have been sterilized before release."

On the other hand, the July 14 editorial wholly endorses Dr Alexander's position, a major tenet of which is the fact that medical practices of exactly this sort may lead to that situation in which criteria for sterilization reflect political as well as medical motivations.

It is difficult for me to reconcile the Danish position with the warnings expressed by Dr Alexander. I should appreciate the comments of the editors on the points raised in the two editorials cited.

I take this opportunity, in passing, of commending the *Journal* for its continued policy of fairness and open-mindedness, which has made it one of the few medical organs that

have maintained objectivity in the sociologic as well as the scientific aspects of medicine

E. RICHARD WEINERMAN, M.D.

Visiting Associate Professor of Medical Economics

University of California School of Public Health
Berkeley, California

Note The Herstedvester editorial referred to by Dr. Weinerman committed the *Journal* to the extent of saying that the penal code of Denmark had much to recommend it. The editors did not thereby intend to commit themselves to either approval or disapproval of the particular point that Dr. Weinerman has stressed—that of castration as a condition of release of sex offenders.

The address by Dean Sperry published in the *Journal* for December 23, 1948, is recalled, in which he states that often the choice between the right course and the wrong one is not between black and white but between two shades of gray, both of which have points that recommend them.—Ed

BOOK REVIEWS

Textbook for Almoners. By Dorothy Manchec, almoner, St. Mary's Hospital, London. With a foreword by Sir Alfred B. Howitt, C.V.O., M.D., president, Institute of Almoners. 8°, cloth, 466 pp., with 49 diagrams and drawings. Baltimore: Williams and Wilkins Company, 1947. \$7.50.

In ancient times an almoner was the keeper of the purse, although at St. Bartholomew's Hospital in London the "Almoners," later called the House Committee, originally had the duty of interviewing all patients and admitting them to the hospital at discretion. Today the almoners in England are the medical social workers, as they are known in the United States. Sir Charles Loch, the secretary of the Family Welfare Association, formerly the Charity Organization Society, was the founder of the modern almoning profession. As early as 1885 he became interested in social work in hospitals, and in 1894 he succeeded in interesting his organization in the matter, in 1895 Miss Mary Stewart, a secretary of the Charity Organization Society, was appointed to the position of almoner at the Royal Free Hospital, the first almoner to be appointed in England. Her duties as laid down by the hospital board were to prevent any abuse of the hospital by persons able to pay for medical treatment, and to refer destitute patients to the proper authorities. It is only within recent years that hospitals in the United States have taken steps to control this abuse. The movement has steadily progressed until today in England there is a well established profession of almoning with its governing institute, composed of management and labor, broadly speaking, and its own hospital-almoners' association. In October, 1945 the *Interim Report of the Social and Preventive Medicine Committee of the Royal College of Physicians* was published. It confines the functions of the almoners to medical social work. The Institute stated that the chief function of an almoner shall be medicosocial work in its various aspects. They may assume as required certain administrative responsibilities, such as checking patients' ability to pay fees.

This book constitutes a valuable document concerning the development of medical social work in England. The text is divided into four parts: origin and growth of the almoner service, social legislation, financial assistance, and social aspects of disease. In the last part are discussed the various subdivisions of the practice of medicine.

The text was printed in Great Britain and is well done with a good type on a light, soft non-glare paper. Although the book is dated 1947, it was not distributed until recently in the United States. Miss Manchec is the author of two previous small books: *Social Service in a General Hospital* and *Social Service in the Clinic for Venereal Disease*. Although the text is based on London experience and on British legislation and regulations, the book should be in all collections on social service work, both medical and general.

Medicine throughout Antiquity. By Benjamin L. Gordon, M.D. With a foreword by Dr. Max Neuburger. 8°, cloth, 818 pp., with 157 illustrations. Philadelphia: F. A. Davis Company, 1949. \$6.00.

Dr. Gordon has traced the history of early medicine from the beginning of man, reputed to be about half a million years B.C., to the end of the Greco-Roman period, terminating

with the fall of Rome in 476 A.D. He has compiled from all available widely recognized sources the facts pertinent to his subject. The work has been divided into two main parts: the prehistoric and protohistoric periods, and the Greco-Roman period. This last period is susceptible to a fuller exposition because of the extensive literature on it. The first period, the prehistoric, begins with the first appearance of man and ends when history began to be recorded, here one must depend on archaeology, paleology and palaeopathology for facts revealed by human fossils, cave and stone drawings and paintings, and on primitive instruments. In the protohistoric period the facts are drawn from such documents as the code of Hammurabi, the Old Testament of the Bible and the works of Homer, this period extended until the rise of the Ionian school of philosophy about 600 B.C. The second period begins with Thales of Miletus, of the Grecian school of philosophers. In the first division of his work the author includes material on paleology and evolution, on the primitive concepts of disease and death, and on the early concepts of nature, and on the Ionian and Athenian schools of philosophy as necessary for an understanding of early medicine. In this chapter on early man one notices the omission of Osborn's great work, *Men of the Old Stone Age*. Likewise, the outstanding work of Hovorka and Kronfeld, *Folkmedicine*, seems to have been missed. After the general chapters the medicine of the various races is discussed, beginning with the Assyrians and Babylonians and including the ancient Egyptians, Hebrew medicine, Persians, Hindus, Japanese and the prehistoric American Indians. The last two chapters of the book are on Talmudic medicine, and they would better have been placed with the one on Hebrew medicine. Many persons confuse the meaning of the words Hebrew and Jew. Modern scholars limit the word Hebrew to the language and refer to the race as the Jews. There is a looseness in dating Jewish medicine. In the opening paragraphs on ancient "Hebrew medicine" the time of Abraham is noted in one place as 2000 B.C. and in another as 2500 B.C. Likewise, the period of the Talmud is not dated. The second section of the work is divided into two parts on Grecian and Roman medicine, beginning with chapters on Aesculapian and Homeric medicine, on the influence of philosophy on medicine and on the Ionian and Eleatic schools of philosophy and on the medical philosophers and practitioners. The whole subject is covered from Hippocrates to the empirics. The part on Roman medicine considers the period from the Methodic school to Galen. The vivid description by Ovid of the pestilence that raged in Rome during the period of his life, 43 B.C. to 17 A.D., is given in an English translation. It is noted that the famous description by Thucydides of the plague at Athens is not mentioned. There are a number of typographic errors in the text, such as "Calumella" for "Columella" and "Gellius" for "Aulus Gellius." The various chapters are documented with lists of references and notes to passages in the text. The references in many cases are poorly cited, omitting edition, place and date and, in some cases, the title. There is a long index, but it does not contain all the names in the text or references. The type, printing and illustrations are excellent, but the coated paper makes the volume too heavy for continuous reading. The material on Jewish medicine is valuable because it is in English and easier to use than the monumental work of Preuss, *Biblisch-talmudische Medizin*. The history should be in all medical libraries and medical-history collections.

Hindu Medicine. By Henry R. Zimmer, Ph.D. Edited with a foreword and preface by Ludwig Edelstein, Ph.D. 12°, cloth, 203 pp. Baltimore: Johns Hopkins Press, 1948.

The late Professor Zimmer, in 1940, delivered the seventh course of the Hideyo Noguchi lectures at Johns Hopkins Institute of the History of Medicine. He was preparing the material for publication, after making considerable revision, enlargement and rearrangement, when he died suddenly early in 1943. He had completed the first lecture and the greater part of the second lecture, but the third lecture was represented by a great deal of fragmentary memoranda. It was quite evident from a study of the material that the work, as originally planned, could not be published. Professor Edelstein and Mrs. Zimmer considered the matter and finally decided to print the first two lectures from the manuscript without alteration. The third lecture represents a reconstruction, as far as possible, of the author's ideas and concepts of

certain diseases and cures and two appendixes, comprising the translation of the tables of contents of the *Susruta-Samhita* and the *Encyclopedia of the Elephant Man*. This reconstruction, which was made by Dr Edelstein, is contained in a long preface of fifty-six pages. Professor Zimmer had no idea of competing with Jolly's scholarly work on Indian medicine contained in the *Encyclopedia of Indo-Aryan Research*, Vol 3 Strassburg, 1901. He was endeavoring to interpret Hindu culture so as to understand its meaning in its own terms and to ascertain its value for men today. The two lectures printed are entitled "Medical Tradition and the Hindu Physician" and "The Human Body: Its forces and resources." The text is concluded with notes to the introduction and the lectures, and an index of passages from the classical Hindu texts. The small volume is well published but lacks an index to the contents. It should be in all medical-history collections.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Biological Reactions Caused by Electric Currents and by X-Rays. A theoretical study of the phenomena of excitation in the nerve by different electric currents and of the biological reactions caused by X-Rays, both based upon a common principle. By J. Th. van der Werff, M.D., D.Sc. 8°, cloth, 203 pp., with 38 illustrations. New York: Elsevier Publishing Company, Incorporated, 1948. \$5.00.

This monograph is a highly technical presentation of its subject, written for physiologists and radiologists. Although the study is biologic, the author has made an extensive use of mathematics. However, two of the highly technical parts are concluded with chapters entitled "Summary" and "Conclusions," in which all the mathematics, except the fundamental equations, have been left out. The text is divided into three parts: the first consists of a general introduction and essentials (including a hypothetical equation of metabolism). In this part the author points out that the phenomena of excitation caused by electric currents, especially those of excitation of the nerve, and the biologic reactions caused by x-rays are analogous to such an extent that it is highly probable that they may be explained from a common principle. Likewise in this part, the author has tried to formulate this principle but has had to resort to bigger mathematics without which the formulation could not have been made. The second part discusses the electric excitation of the nerve and the third, biologic relations caused by x and gamma rays. The pertinent literature is referred to throughout the text and instead of a regular bibliography, there is a list of the authors mentioned and the sources of their articles. There are also author and subject indexes. The book is well published in every way. The comparatively high price for such a small volume is justified by the great number of intricate mathematical formulas. The volume should be in all collections on radiology and physiology.

Diseases of the Ear, Nose, and Throat. By Douglas G. Carruthers, M.B., Ch.M. (Sydney) consulting ear nose and throat surgeon, Canterbury District Memorial Hospital, Sydney. Second edition. 8°, cloth, 344 pp., with 140 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$7.00.

The first edition of this small textbook for students and general practitioners was published in Sydney in 1943. This second edition has been revised and the use of penicillin and the sulfonamides has been included as well as the newest form of treatment for tropical otitis externa. The technique for tonsillectomy is given in detail. There is a "pharmaceutical" index, comprising standard recipes, and also an index of subjects. The text was printed in Great Britain and is well done. The publication on the whole is excellent.

Reprints from the Oxford-Loose-Leaf Medicine. By Walter C. Alvarez and others. 8°, paper. New York: Oxford University Press, Incorporated, 1948. Not for sale.

This collection of reprints comprises twenty-one articles taken from the latest edition of the *Oxford System of Medicine*. They cover the whole field of medicine and are supplied only to subscribers to the complete work and are not for sale. They are valuable to libraries because they offer in a single form various worthwhile articles that may be lent, and the bound volumes of the system may thus be kept available for reference.

Veterans Administration Technical Bulletin, Vol. I 1946 and 1947. 4° cloth, 240 pp. Washington, 1948. Vol. II, 1948. 4°, cloth, 168 pp. Washington, 1949.

These two volumes for 1946-1948 contain thirty-six articles of a clinical character covering the whole field of practical medicine. They are intended primarily for the staff of the Veterans Administration. They are produced in an excellent manner by offset printing and are substantially and well bound. They should be in all reference medical libraries.

Surgery of the Hand. By Sterling Bunnell, M.D., consultant in hand surgery to the Surgeon General and licentiate of American Board of General Surgery and Plastic Surgery. First edition. 4°, cloth, 930 pp., with 779 illustrations. Philadelphia: J. B. Lippincott Company, 1948. \$16.00.

This second edition of a standard special work has been revised to bring its contents up to date since the publication of the first edition in 1944. Considerable material has been added, mostly to the chapters on reconstruction injuries, infection and tumors. Lists of references are appended to the various chapters. The book is profusely and well illustrated. There is a good index. The volume is recommended for all medical libraries and it should prove valuable to surgeons interested in the hand.

Cardiology. By William Evans, M.D., D.Sc., F.R.C.P., physician to the cardiac department of the London Hospital, physician to outpatients of the National Heart Hospital and consulting cardiologist to the Royal Navy. 8°, cloth, 330 pp., with 269 illustrations and 15 tables. New York: Paul B. Hoeber, Incorporated, 1948. \$7.50.

This condensed treatise is intended for the medical student who desires a concise book to prepare him for his final examinations. The work is based on a series of lectures given to postgraduate students at the London Hospital. The material is well organized. The text was printed in Great Britain with a good type. There is considerable waste of paper in the make-up of the index. It is surprising how many British books are being imported in pages into the United States and then bound and distributed by various publishers, in preference to promotion of works by native authors. Of course this practice is helping Great Britain in its export program.

Cancer of the Esophagus and Gastric Cardia. Edited by George T. Pack, M.D., clinical professor of surgery, New York Medical College and attending surgeon, Memorial Hospital for Cancer and Allied Diseases. 8°, cloth, 192 pp., with illustrations. St. Louis: C. V. Mosby Company, 1949. \$5.00.

This monograph is a reprint of a symposium originally published in *Surgery* for June 1948. Eighteen specialists presented eleven articles, three of which discuss the transthoracic and transdiaphragmatic methods. The publishing is excellent. The book should prove valuable to surgeons interested in the subject, and libraries could well substitute it for the bound volume of the periodical.

Shock And allied forms of failure of the circulation. By H. A. Davis, M.D., C.M., associate professor of surgery and director, Division of Surgery, Graduate School of Medicine, College of Medical Evangelists, Los Angeles Division, senior attending surgeon, Los Angeles County General Hospital and White Memorial Hospital and visiting surgeon, Cedars of Lebanon Hospital and California Hospital. 8°, cloth, 595 pp., with 55 illustrations. New York: Grune and Stratton, 1949. \$12.00.

This comprehensive monograph considers shock in all its varying aspects. Beginning with a historical introduction including classification, the text proceeds from physiology,

have maintained objectivity in the sociologic as well as the scientific aspects of medicine.

E. RICHARD WEINERMAN, M.D.

Visiting Associate Professor of Medical Economics

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Berkeley, California

Note The Herstedvester editorial referred to by Dr. Weinerman committed the *Journal* to the extent of saying that the penal code of Denmark had much to recommend it. The editors did not thereby intend to commit themselves to either approval or disapproval of the particular point that Dr. Weinerman has stressed—that of castration as a condition of release of sex offenders.

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BOOK REVIEWS

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In ancient times an almoner was the keeper of the purse, although at St. Bartholomew's Hospital in London the "Almoners," later called the House Committee, originally had the duty of interviewing all patients and admitting them to the hospital at discretion. Today the almoners in England are the medical social workers, as they are known in the United States. Sir Charles Loch, the secretary of the Family Welfare Association, formerly the Charity Organization Society, was the founder of the modern almoning profession. As early as 1885 he became interested in social work in hospitals, and in 1894 he succeeded in interesting his organization in the matter, in 1895 Miss Mary Stewart, a secretary of the Charity Organization Society, was appointed to the position of almoner at the Royal Free Hospital, the first almoner to be appointed in England. Her duties as laid down by the hospital board were to prevent any abuse of the hospital by persons able to pay for medical treatment, and to refer destitute patients to the proper authorities. It is only within recent years that hospitals in the United States have taken steps to control this abuse. The movement has steadily progressed until today in England there is a well established profession of almoning with its governing institute, composed of management and labor, broadly speaking, and its own hospital-almoners' association. In October, 1945 the *Interim Report of the Social and Preventive Medicine Committee of the Royal College of Physicians* was published. It confines the functions of the almoners to medical social work. The Institute stated that the chief function of an almoner shall be medicosocial work in its various aspects. They may assume as required certain administrative responsibilities, such as checking patients' ability to pay fees.

This book constitutes a valuable document concerning the development of medical social work in England. The text is divided into four parts: origin and growth of the almoner service, social legislation, financial assistance, and social aspects of disease. In the last part are discussed the various subdivisions of the practice of medicine.

The text was printed in Great Britain and is well done with a good type on a light, soft non-glare paper. Although the book is dated 1947, it was not distributed until recently in the United States. Miss Manchée is the author of two previous small books: *Social Service in a General Hospital* and *Social Service in the Clinic for Venereal Disease*. Although the text is based on London experience and on British legislation and regulations, the book should be in all collections on social service work, both medical and general.

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Dr. Gordon has traced the history of early medicine from the beginning of man, reputed to be about half a million years B.C., to the end of the Greco-Roman period, terminating

with the fall of Rome in 476 A.D. He has compiled from all available widely recognized sources the facts pertinent to his subject. The work has been divided into two main parts: the prehistoric and protohistoric periods, and the Greco-Roman period. This last period is susceptible to a fuller exposition because of the extensive literature on it. The first period, the prehistoric, begins with the first appearance of man and ends when history began to be recorded, here one must depend on archeology, paleology and paleopathology for facts revealed by human fossils, cave and stone drawings and paintings, and on primitive instruments. In the protohistoric period the facts are drawn from such documents as the code of Hammurabi, the Old Testament of the Bible and the works of Homer, this period extended until the rise of the Ionian school of philosophy about 600 B.C. The second period begins with Thales of Miletus, of the Grecian school of philosophers. In the first division of his work the author includes material on paleology and evolution, on the primitive concepts of disease and death, and on the early concepts of nature, and on the Ionian and Athenian schools of philosophy as necessary for an understanding of early medicine. In the chapter on early man one notices the omission of Osborn's great work, *Men of the Old Stone Age*. Likewise, the outstanding work of Hovorka and Kronfeld, *Folkmedicine*, seems to have been missed. After the general chapters the medicine of the various races is discussed, beginning with the Assyrians and Babylonians and including the ancient Egyptians, Hebrew medicine, Persians, Hindus, Japanese and the prehistoric American Indians. The last two chapters of the book are on Talmudic medicine, and they would better have been placed with the one on Hebrew medicine. Many persons confuse the meaning of the words Hebrew and Jew. Modern scholars limit the word Hebrew to the language and refer to the race as the Jews. There is a looseness in dating Jewish medicine. In the opening paragraphs on ancient "Hebrew medicine" the time of Abraham is noted in one place as 2000 B.C. and in another as 2500 B.C. Likewise, the period of the Talmud is not dated. The second section of the work is divided into two parts on Grecian and Roman medicine, beginning with chapters on Aesculapian and Homeric medicine, on the influence of philosophy on medicine and on the Ionian and Eleatic schools of philosophy and on the medical philosophers and practitioners. The whole subject is covered from Hippocrates to the empires. The part on Roman medicine considers the period from the Methodic school to Galen. The vivid description by Ovid of the pestilence that raged in Rome during the period of his life, 43 B.C. to 17 A.D., is given in an English translation. It is noted that the famous description by Thucydides of the plague at Athens is not mentioned. There are a number of typographic errors in the text, such as "Calumella" for "Columella" and "Gellius" for "Aulus Gellius." The various chapters are documented with lists of references and notes to passages in the text. The references in many cases are poorly cited, omitting edition, place and date and, in some cases, the title. There is a lone index, but it does not contain all the names in the text or references. The type, printing and illustrations are excellent but the coated paper makes the volume too heavy for continuous reading. The material on Jewish medicine is valuable because it is in English and easier to use than the monumental work of Preuss, *Biblisch-talmudische Medizin*. The history should be in all medical libraries and medical-history collections.

Hindu Medicine. By Henry R. Zimmer, Ph.D. Edited with a foreword and preface by Ludwig Edelstein, Ph.D. 12°, cloth, 203 pp. Baltimore: Johns Hopkins Press, 1948.

The late Professor Zimmer, in 1940, delivered the seventh course of the Hideo Noguchi lectures at Johns Hopkins Institute of the History of Medicine. He was preparing the material for publication, after making considerable revision, enlargement and rearrangement, when he died suddenly in 1943. He had completed the first lecture and the early part of the second lecture, but the third lecture was greater part of the second lecture, but the third lecture was represented by a great deal of fragmentary memoranda. It was quite evident from a study of the material that the work, originally planned, could not be published. Professor Edelstein and Mrs. Zimmer considered the matter and finally decided to print the first two lectures from the manuscript without alteration. The third lecture represents a reconstruction, as far as possible, of the author's ideas and concepts of

certain diseases and cures and two appendixes, comprising the translation of the tables of contents of the *Susruta-Samhita* and the *Encyclopedia of the Elephant Man*. This reconstruction, which was made by Dr Edelstein, is contained in a long preface of fifty-six pages. Professor Zimmer had no idea of competing with Jolly's scholarly work on Indian medicine contained in the *Encyclopedia of Indo-Aryan Research*, Vol 3 Strassburg, 1901. He was endeavoring to interpret Hindu culture so as to understand its meaning in its own terms and to ascertain its value for men today. The two lectures printed are entitled "Medical Tradition and the Hindu Physician" and "The Human Body: Its forces and resources." The text is concluded with notes to the introduction and the lectures, and an index of passages from the classical Hindu texts. The small volume is well published but lacks an index to the contents. It should be in all medical-history collections.

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This monograph is a highly technical presentation of its subject, written for physiologists and radiologists. Although the study is biologic, the author has made an extensive use of mathematics. However, two of the highly technical parts are concluded with chapters entitled "Summary" and "Conclusions," in which all the mathematics, except the fundamental equations, have been left out. The text is divided into three parts: the first consists of a general introduction and essentials (including a hypothetical equation of metabolism). In this part the author points out that the phenomena of excitation caused by electric currents, especially those of excitation of the nerve, and the biologic reactions caused by x-rays are analogous to such an extent that it is highly probable that they may be explained from a common principle. Likewise, in this part, the author has tried to formulate this principle but has had to resort to higher mathematics without which the formulation could not have been made. The second part discusses the electric excitation of the nerve and the third, biologic relations caused by x and gamma rays. The pertinent literature is referred to throughout the text and instead of a regular bibliography, there is a list of the authors mentioned and the sources of their articles. There are also author and subject indexes. The book is well published in every way. The comparatively high price for such a small volume is justified by the great number of intricate mathematical formulas. The volume should be in all collections on radiology and physiology.

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The first edition of this small textbook for students and general practitioners was published in Sydney in 1943. This second edition has been revised and the use of penicillin and the sulfonamides has been included as well as the newest form of treatment for tropical otitis externa. The technique for tonsillectomy is given in detail. There is a 'pharmaceutical' index, comprising standard recipes, and also an index of subjects. The text was printed in Great Britain and is well done. The publication on the whole is excellent.

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This collection of reprints comprises twenty-one articles taken from the latest edition of the *Oxford System of Medicine*. They cover the whole field of medicine and are supplied only to subscribers to the complete work and are not for sale. They are valuable to libraries because they offer in a single form various worthwhile articles that may be lent, and the bound volumes of the system may thus be kept available for reference.

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These two volumes for 1946-1948 contain thirty-six articles of a clinical character covering the whole field of practical medicine. They are intended primarily for the staff of the Veterans Administration. They are produced in an excellent manner by offset printing and are substantially and well bound. They should be in all reference medical libraries.

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This second edition of a standard special work has been revised to bring its contents up to date since the publication of the first edition in 1944. Considerable material has been added mostly to the chapters on reconstruction, injuries, infection and tumors. Lists of references are appended to the various chapters. The book is profusely and well illustrated. There is a good index. The volume is recommended for all medical libraries and it should prove valuable to surgeons interested in the hand.

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This comprehensive monograph considers shock in all its varying aspects. Beginning with a historical introduction, including classification, the text proceeds from physiology,

have maintained objectivity in the sociologic as well as the scientific aspects of medicine

L. RICHARD WEINERMAN, M.D.

Visiting Associate Professor of Medical Economics

University of California School of Public Health
Berkeley, California

Note The Herstedvester editorial referred to by Dr. Weinerman committed the *Journal* to the extent of saying that the penal code of Denmark had much to recommend it. The editors did not thereby intend to commit themselves to either approval or disapproval of the particular point that Dr. Weinerman has stressed—that of castration as a condition of release of sex offenders.

The address by Dean Sperry published in the *Journal* for December 23, 1948, is recalled, in which he states that often the choice between the right course and the wrong one is not between black and white but between two shades of gray, both of which have points that recommend them.—Ed

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This comprehensive monograph considers shock in all its varying aspects. Beginning with a historical introduction, including classification, the text proceeds from physiology,

biochemistry, diagnosis and pathology, through the various types of shock, and ends with treatment. The large literature on the subject is reviewed throughout the text. Long bibliographies are appended to the various chapters. There is a good index. The type, printing and illustrations are excellent. The volume is very heavy for its size, owing to the use of a hard filled paper, probably justified by the number of reproductions of microscopical slides. The book is recommended for all medical libraries and should prove valuable to surgeons and other persons interested in shock.

The Basis of Chemotherapy By Thomas S. Work, Ph.D., research staff, National Institute for Medical Research, London, and Elizabeth Work, Ph.D., research staff, Department of Chemical Pathology, University College Hospital Medical School, London. 8°, cloth, 435 pp., with 42 illustrations and 38 tables. New York: Interscience Publishers, Incorporated, 1948. \$6.50.

Here is another British book, imported in sheets and bound and distributed in the United States, but it is a good book and merits serious consideration. The authors have attempted to weld many diverse sciences into a single pattern in order to find a basis for chemotherapy. They have used the resources of organic and physical chemistry, biochemistry, bacteriology, pharmacology and therapeutics, and have analyzed and reviewed the pertinent and current literature in all these fields. The bibliography appended to the text comprises fifty-four pages. After a historical introduction, the chapters deal with cell metabolism, essential metabolites, enzyme inhibition, drug antagonism and resistance, and the relation of structure and activity of drugs. There is a good index, and the book is well printed. It should be in all reference collections in medical and scientific libraries.

The Business Side of Medical Practice By Theodore Wiprud, executive director and secretary, Medical Society of The District of Columbia, and managing editor, *Medical Annals of the District of Columbia*. Second edition. 12°, cloth, 232 pp., with 23 illustrations. Philadelphia: W. B. Saunders Company, 1949. \$3.50.

The first edition of this manual was published in 1937. This edition has been revised in part, and some of the text has been entirely rewritten and other portions expanded. New chapters on opportunities for medical leadership, group medical practice and the future of the doctor have been included in the second edition. A competent lawyer reviewed the material on the legal aspects of medical practice. There is a good index, and the book is well published. This important volume should be in all medical libraries and in the offices of all physicians.

Ghosts of the Air-Waves By Antonio L. Tauro. 12°, cloth, 165 pp. Boston: Meador Publishing Company, 1949. \$2.00.

This novel deals with the problem of unlawful abortion.

Mayo Clinic Diet Manual By the Committee on Dietetics of the Mayo Clinic. 8°, paper, 329 pp. Philadelphia: W. B. Saunders Company, 1949. \$4.00.

This manual outlines the general and special dietary procedures used in the Mayo Clinic and Mayo Foundation and the hospitals of Rochester, Minnesota, represented on the Mayo Clinic committee. In addition to the various diets an appendix contains a number of tables on foods and their special contents and on their composition, standard diabetic diets for children and for adults and height-weight-age tables for men and women. Originally, the material was mimeographed, but in this third edition it has been printed and made available to dietitians outside Rochester. A detailed table of contents takes the place of an index.

NOTICES

ANNOUNCEMENTS

Dr. Jacob B. Burke announces the opening of an office at 162 Shurtleff Street, Chelsea, for the practice of obstetrics and gynecology.

Dr. Max G. Carter announces the opening of an office at 442 Temple Street, New Haven, Connecticut, for the practice of thoracic and cardiovascular surgery.

MASSACHUSETTS CHAPTER OF AMERICAN ACADEMY OF GENERAL PRACTICE

The fall clinical meeting of the Massachusetts Chapter of the American Academy of General Practice will be held in Boston on Wednesday, October 19. The morning will be spent at clinics at the Massachusetts General Hospital, with a luncheon, afternoon papers and banquet at the Hotel Punta.

More complete details will be furnished later.

MASSACHUSETTS PSYCHIATRIC SOCIETY

The annual meeting of the Massachusetts Psychiatric Society will be held at the Hotel Sheraton, Boston, on Friday, October 28, at 7:00 p.m. The speaker will be Carl A. L. Binger, M.D., of New York City, assistant professor of clinical psychiatry at Cornell University Medical College, and formerly United States representative to the International Congress at London in 1948.

This is a dinner meeting, and reservations will be accepted from members of the medical and allied professions.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held in Boston on Wednesday, September 28.

PROGRAM

- 11:00 a.m. - 1:00 p.m. Presentation of cases illustrating research in therapy of disseminated cancer. Dr. Sidney Farber and staff. Amphitheater, Peter Bent Brigham Hospital.
- 2:30 - 4:30 p.m. Clinical sessions conducted by Dr. Allan M. Butler and associates. Amphitheater of Building C, Harvard Medical School.
- 5:30 p.m. Refreshments. Longwood Towers.
- 6:30 p.m. Dinner. Longwood Towers (charge, \$3.25).
- 7:30 p.m. Advances in the Therapy of Infectious Diseases with the Newer Antibiotics. Dr. Emanuel B. Schoenbach, associate professor of preventive medicine and assistant professor of medicine, Johns Hopkins University School of Medicine, and physician, Johns Hopkins Hospital.

TUBERCULOSIS REHABILITATION SOCIETY

The fall meeting of the Tuberculosis Rehabilitation Society will be held at the Cedarcrest Sanatorium, Newington, Connecticut, on Friday, October 14.

The Society was organized in the spring of 1949 with a membership covering the entire New England area. Its object is the promotion of tuberculosis rehabilitation, with special reference to the exchange of technical information, the promotion of interagency and interstate relations, the development of standards for procedures and personnel in this work and promotion of publicity of tuberculosis rehabilitation.

UROLOGY AWARD

The American Urological Association offers an annual award of \$1000 (first prize of \$500, second prize \$300 and third prize \$200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals. The first-prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Washington, D. C., May 29 to June 1, 1950.

Full particulars may be obtained from the secretary, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, New Jersey. Essays must be in his hands before February 20, 1950.

(Notices concluded on page xv)

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HOME ACCIDENTS IN MASSACHUSETTS*

A Study in the Epidemiology of Trauma

HELEN L. ROBERTS, M.D.,† AND JOHN E. GORDON, M.D.‡

BOSTON

SELECTED features of a comparative study of accident mortality in Massachusetts and in the United States are presented here to illustrate a serious community health problem that receives too little attention. The direct objective is to determine by epidemiologic analysis the features of accident prevention that warrant special consideration in Massachusetts. We are keenly aware that to

population in 1918 to 69.7 in 1947,¹ the relative importance of accidents as a cause of death has increased, owing to improved control of other diseases. Deaths from accidents ranked fourth in 1946 in both Massachusetts and in the United States (Fig. 1), as compared with sixth position in 1935.¹

Massachusetts has a considerably lower rate than the country as a whole. The provisional rates by

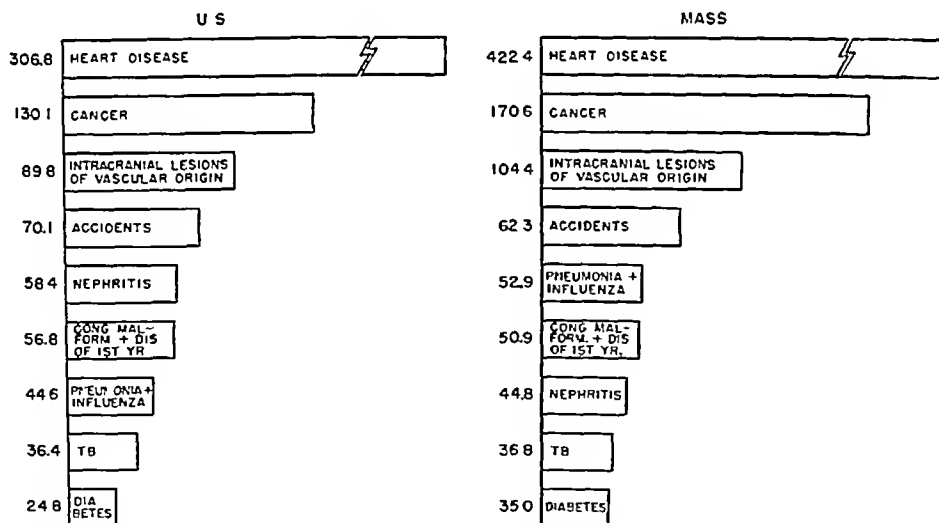


FIGURE 1 Chief Causes of Death, United States² and Massachusetts,³ 1946 (Rates per 100,000 Population)

study accidental deaths without concurrent attention to temporary and permanent disability is to under-rate greatly the medical, economic and social seriousness of the problem. In the absence of specific morbidity data, deaths necessarily serve as the index.

Although the total death rate from accidents in the United States decreased from 85.5 per 100,000

states for 1947, published by the National Safety Council,¹ give Massachusetts an enviable comparative standing, since only Connecticut, Rhode Island and New Jersey had better records. The favorable rates of recent years are no isolated circumstance. Figure 2 shows that since 1913, the death rate from accidents has been lower for Massachusetts than for the United States generally in every year except 1942, when Massachusetts suffered the Cocoanut Grove disaster. The data suggest that, in comparison with other regions, effective control measures

*From the Harvard School of Public Health departments of Public Health Practice and Epidemiology.

†Associate in public-health practice.

‡Professor of preventive medicine and epidemiology.

are already in operation or, alternatively, that citizens of the Commonwealth are, by reason of training, age or environment, more accident resistant than the residents of most other states. Unfortu-

with rates varying between 48.0 and 53.9 per 100,000 population.⁴

If accidents are divided into classes by place of occurrence (Fig. 4) the fatal accidents that occur in

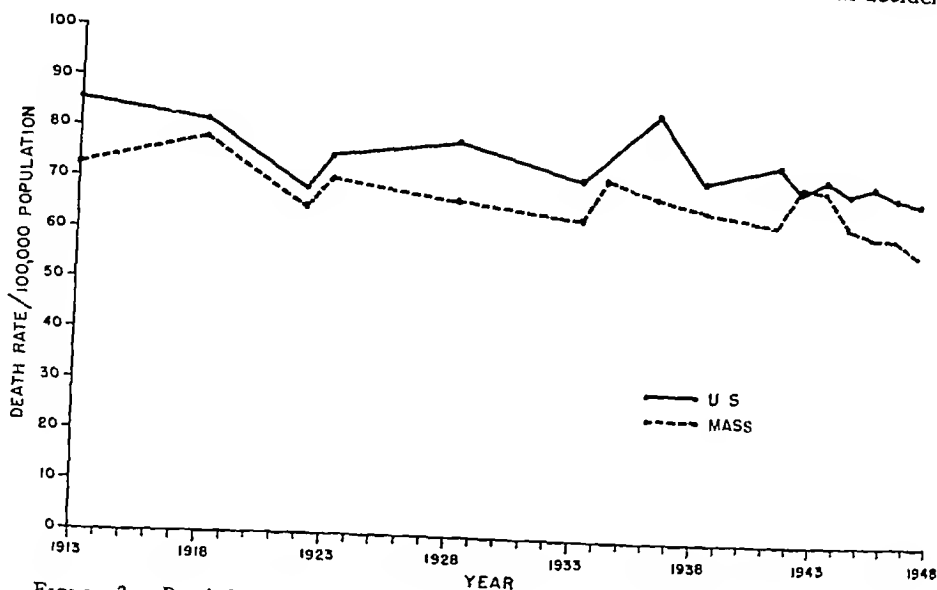


FIGURE 2 Death Rate from All Accidents, Massachusetts² and United States,¹ 1913-1947

nately, the situation is not so satisfying when the rates for Massachusetts are examined more precisely.

Since 1923 the Commonwealth has had a significantly lower motor-vehicle accident death rate than the United States as a whole.³ Total accidental deaths, other than motor vehicle (Fig. 3), demon-

homes are proportionately more important in Massachusetts than in the United States generally. By contrast, motor-vehicle accidents were much less important in Massachusetts (20.2 per cent) in 1947 than in the United States as a whole (32.3 per cent). Pedestrian deaths were relatively more im-

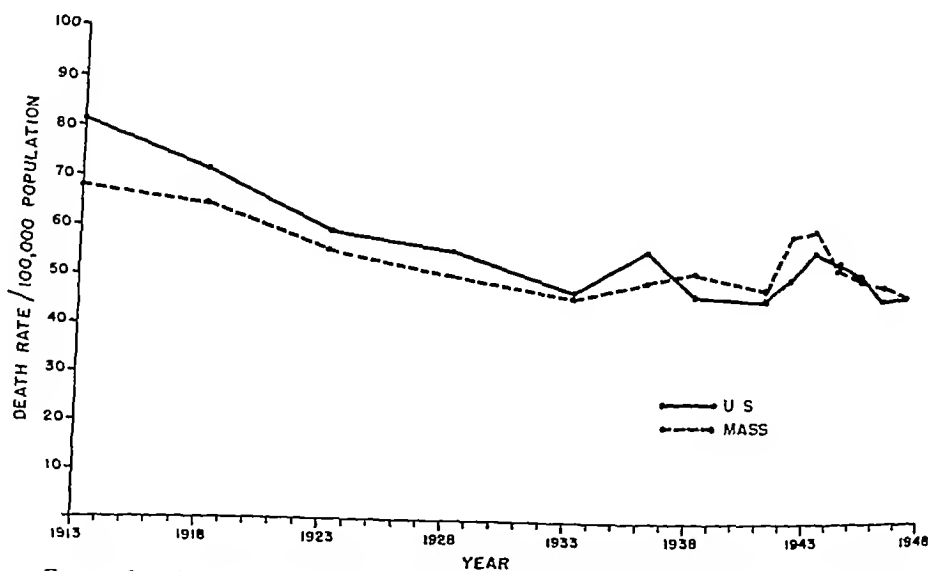


FIGURE 3 Accident Death Rates, Excluding Motor-Vehicle Accidents, Massachusetts² and United States,¹ 1913-1947

strate no significant difference between Massachusetts and the United States over the past twenty years. When states are grouped by accidental deaths other than those involving motor vehicles, Massachusetts is in the third quartile—a group

important, as would be expected in a highly urban community. Accidents in public places (nonmotor vehicle), accounted for a larger percentage of accidental deaths in Massachusetts than in the United States as a whole. Massachusetts had a better than

average record for accidental deaths in the course of occupation

Many environmental and social conditions determine the kind of accidents peculiar to a community. In 1945 only one state exceeded Massachusetts in death rates from falls and crushing injuries.⁸ Serious falls are a function of age, and Massachusetts has an older population. This accounts in part for the observation that falls in 1946 were responsible for 26 per cent of all accidental deaths in the United States, whereas in Massachusetts the figure was 44 per cent.

reason for satisfaction. There is the added consideration that the average experience of as large a geographic area as a state cannot reasonably be used by a community to judge its individual accident problem. Variations in housing, crowding, age distribution and economic levels strongly influence the frequency and kind of accidents.

EPIDEMIOLOGY

Deaths from accidents in the United States in 1947 numbered approximately 100,000. Home acci-

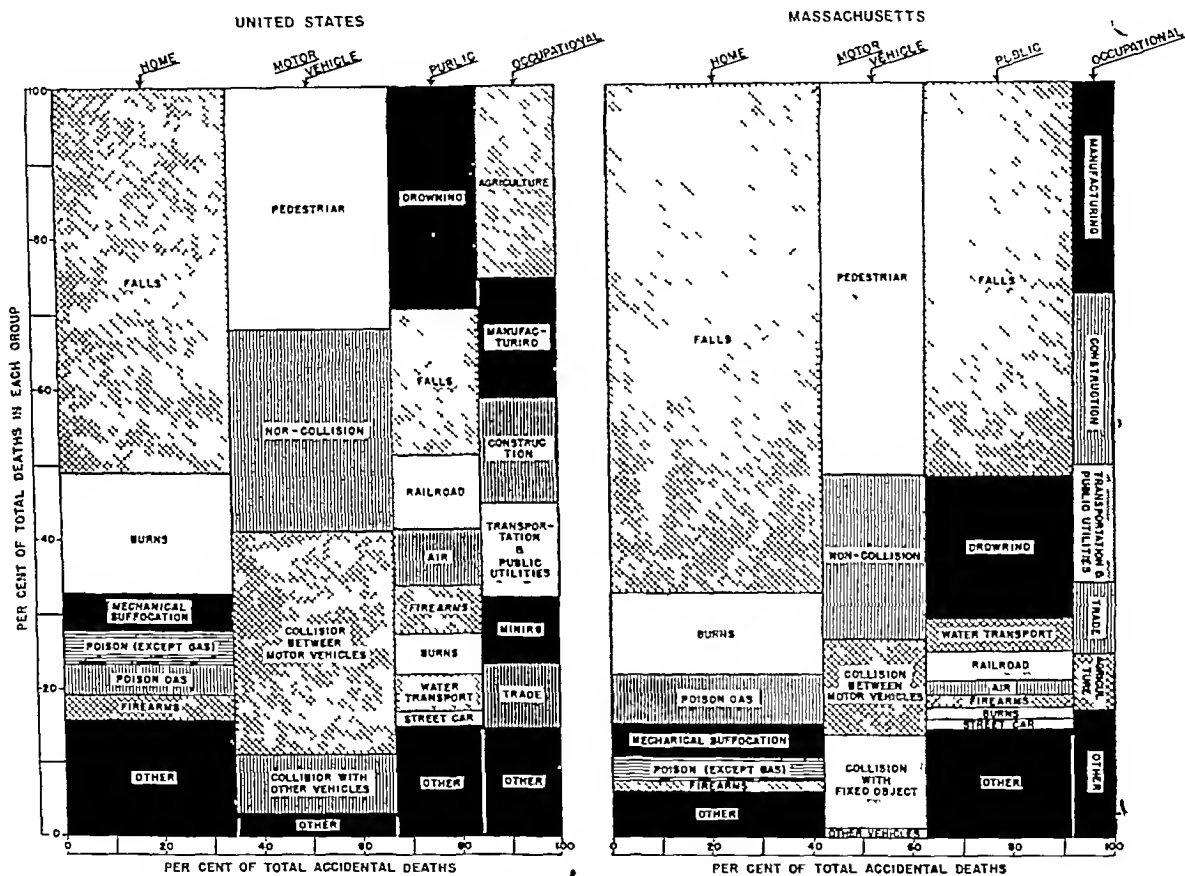


FIGURE 4 Accident Mortality, 1947, by Class and Cause, United States¹ and Massachusetts²
Based on data of Kansas State Board of Health³

Comparison of other epidemiologic variations in accidental deaths, such as seasonal and sex incidence, shows no marked differences between the two regions. The outstanding disparity that calls for special effort in Massachusetts is the excess of home and public accidents (Fig 5), falls being the paramount factor in each. That Massachusetts has a more serious problem, in these respects, is no reason for lack of attention to other areas of accident prevention. No part of the United States has so controlled accident morbidity or mortality in any age group or in any class of accidents as to have great

accidents accounted for more than a third (34,500) of the deaths and half (5,200,000) of the disabling injuries.¹ For every death from a home accident there are approximately 150 disabling injuries, of which 4 result in some permanent defect. No one of the other three classes of accidents — motor-vehicle, public and industrial — is responsible for so many deaths or disabling injuries. Home accidents alone were the ninth leading cause of death in the United States in 1946.²

The trend of home accidents, as judged by deaths, has shown remarkably little fluctuation from 1930

are already in operation or, alternatively, that citizens of the Commonwealth are, by reason of training, age or environment, more accident resistant than the residents of most other states. Unfortun-

with rates varying between 48.0 and 53.9 per 100,000 population.⁴

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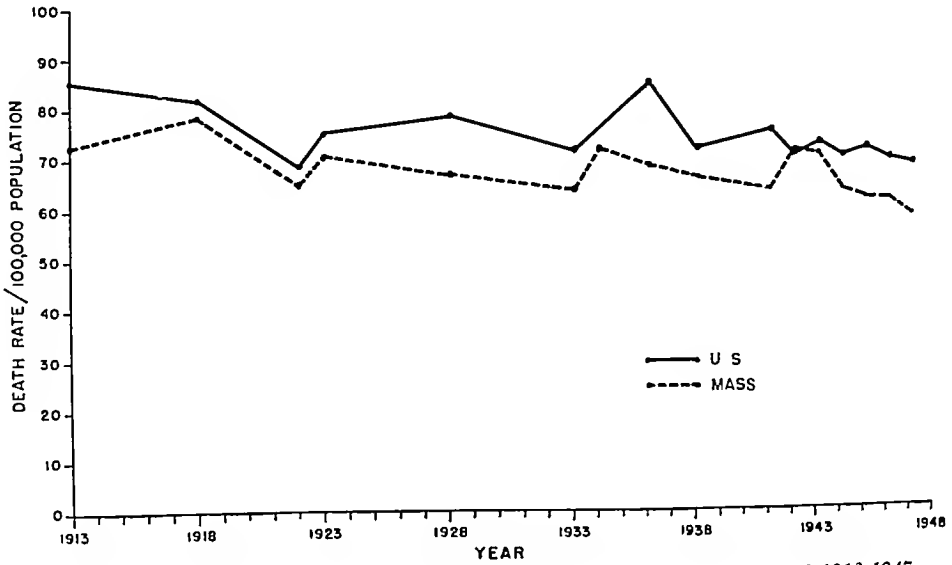


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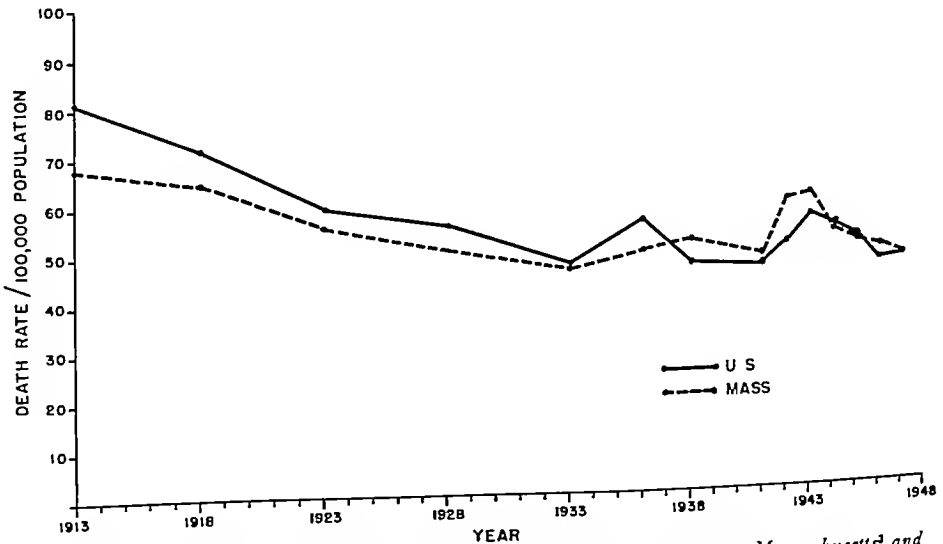


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Much is known about age as a determining host factor. Deaths are most frequent among infants and the aged, not only because they spend most of their time in the home but also because they are least able to guard against an unfavorable environment. In 1946, 70 per cent of all fatal accidents in children under five were home accidents. Rates for infants were three or four times those for older pre-school children. Essentially two thirds of all fatal accidents that affected persons over sixty-five years of age in 1947 were home accidents, the rates being 185.0 as contrasted to 42.4 for children under five.¹ As suggested by Britten et al.,¹⁴ it may be misleading to judge the actual incidence of home accidents on the basis of death or serious disability, because an accident with serious consequences in an aged person may be of little moment for a young adult.

The kinds of fatal accident in the home differ markedly for various age groups. Burns were the most common fatal accident, in the data for the United States, at all ages under forty-five years, with the exception of persons in the age group of fifteen to twenty-four years, in which death from firearms ranked first and burns second. Falls were relatively unimportant among children, but became increasingly prominent after the age of twenty-five years, so that in persons over sixty-five years, 77 per cent of all home-accident deaths in the United States in 1946 were of this nature.¹ The Kansas Accidental Death Report⁹ points succinctly to the fact that falls in the elderly and infirm unduly weight the results. In 1947, in Kansas, 60 per cent of accidental deaths in the home were due to falls, but of these only 5 per cent involved persons under sixty-five years of age and in apparent good health.

Sex, like age, is a significant host factor. Deaths from all accidents, other than motor vehicle, involve males much more frequently throughout life than females. If only disabling home accidents are considered, as in the National Health Survey,¹⁴ males predominate up to the age of twenty-five years, and thereafter, serious home accidents happen more often to females, so that the annual frequency rate for females for all home accidents was almost one and a half times that for males. There are 2 fatal home accidents in elderly females for every 1 among elderly males.

An outstanding sex factor was noted by Brown and his associates¹⁵ in Kansas and Nassau County, Long Island: the number of boys dying in home accidents between the ages of one and fifteen years was twice that for girls, despite the reasonable belief that the hours of exposure were much the same, and certainly no greater for boys.

Environmental Factors

The causal factors arising from the environment have been studied more exhaustively than those of the agent or host. The frequency of fatal home accidents varies markedly from one state to another.

For 27 states reporting in 1947, Missouri had the highest rate, 34.5, and Utah the lowest, 16.8. Evidently the variables in home-accident rates do not correlate with total accident death rates, which were 74.5 for Missouri and a high of 82.9 for Utah. Rates vary more markedly with the concentration and type of population in a given community than with its geographic location. Thus, in 1947, home-accident death rates for urban areas were 31 per 100,000 population, for farm homes 26, but for rural nonfarm regions only 14 per 100,000.¹

Several studies have established various areas within the home as an environmental factor. An analysis of 987 fatal home accidents in Kansas and Nassau County, Long Island,¹ showed that a fourth occurred in the bedroom, because most deaths of infants and the aged were there. The yard and then the kitchen were next, followed by stairs, with other locations much less frequently the site of a fatal home accident. The studies of the Metropolitan Life Insurance Company¹⁶ of nonfatal home accidents showed the kitchen to be the most hazardous home area.

In Massachusetts³ there is a marked seasonal fluctuation in the frequency of home-accident deaths, with recurring peaks in December or January, and low rates in September, as indicated by the years 1945-47. Individual types of home-accident deaths vary markedly with season. Falls, burns of all types and deaths by poisonous gas are more frequent in the winter months, whereas deaths from poisons other than gas and from firearms show little seasonal variation. The influence of various hours of the day or night, holidays, week ends and periods of bad weather is unknown.

A marked correlation between socioeconomic factors and the frequency of home accidents is often assumed, but with little factual data to support the hypothesis. The best information comes from the National Health Survey of 1935-36¹⁴ in which the frequency rate for all home accidents causing disability of at least one week decreased from 6.01 per 1000 persons for families on relief to 4.10 for families with annual incomes of \$1000 to \$1500, and thereafter in the higher income groups a relatively stable rate was attained.

As is true of disease, no one of the three causative factors acts singly to result in the injury or produce the accident. Some one element may predominate, but ordinarily all interact. Since home accidents as a community health problem are primarily the concern of the medical profession and public-health departments, they are approached most readily and most practically by the methods that preventive medicine and public health have utilized for other health problems that affect masses of people — the epidemiologic approach. As applied to home accidents, the epidemiologic method is simply the collection and analysis of all the facts in a given area. The things to be known in terms of mortality and

to 1947. The annual rate, which is usually about 24 per 100,000 population, in seventeen years has not been less than 23, and rarely exceeds 25. An all-time high of 29 occurred in 1936. In 1947 home-accident deaths increased 5 per cent over 1946, and except for 1936, the rate was the highest on record.¹ In this uniform trend, home accidents have not paralleled the improvement shown for accidents as a whole, for industrial accidents, or for motor-vehicle deaths.¹

Six types of accidents are responsible for 85 per cent of home-accident deaths. Falls are numerically

Earlier publications^{7, 8} have shown that accidents follow the same biologic laws as other morbid processes that involve groups of people, and hence are susceptible to the same methods of epidemiologic study so valuable in the communicable diseases and now applied to mass disease in general — to diabetes, cancer and many others.

The collection and arrangement of home-accident data according to etiologic factors that relate to agent, host and environment are believed essential to proper weighting and evaluation. They permit specific preventive measures to be applied to important causes in a given community. This framework is now used to present some of the known epidemiologic facts about home accidents and to gauge the need for the collection of added information.

Etiologic Agents

The usual classification of home accidents by type is useful in describing the mechanism of injury, but does not provide information about the direct causative agent or the activity of the victim at the time of the accident. If the accident is a burn, was it due to smoking in bed, to a child playing with matches in the mother's absence or to defective electrical wiring? The potential number of agents in falls is even greater than that for burns, and to classify all such accidents by mechanism alone is to mask the causative relation of such dissimilar agents as a misplaced toy, structural defects in a building and a hole in a driveway.

A few investigators^{9, 11} have studied specific agents in home accidents, but the knowledge thus gained is far from adequate. No studies have included the home accidents that disable the person for only a day or so. No one has enough data to evaluate the varying importance of a particular agent in different geographic areas or under diverse conditions of living, as in rural and urban regions.

Host Factors

Except for the simpler matters of age and sex, host factors have been largely ignored in home-accident studies, although receiving much attention in motor and industrial accidents. They are increasingly appreciated as significant etiologic factors in all accidents. The analyses published by the Kansas State Board of Health⁹ suggest the importance of existing physical disability, especially in the older age groups. The relation of temporary emotional tensions to home accidents is unknown, as is the role of alcohol and drugs. It is known that some people have an unusual number of accidents in any situation, and that this proneness is unrelated to intelligence, reaction time, experience or physical constitution. Accident proneness has been studied in motor¹² and industrial accidents,¹³ but its part in home accidents has yet to be appraised.

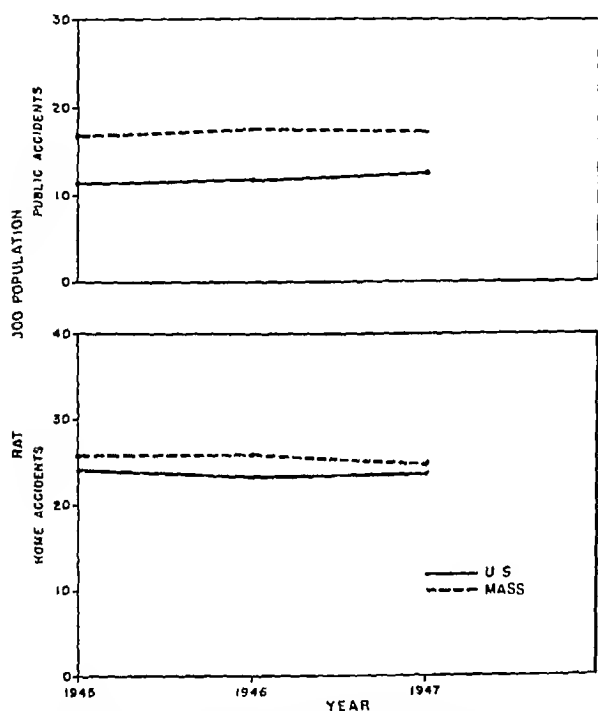


FIGURE 5 Comparison of Accidental Death Rates by Class of Accident, United States¹ and Massachusetts,⁵ 1945-47

the most important, accounting for 17,600 deaths in the United States in 1947, or more than half of all fatal home accidents. This was more than three times the number in the next most frequent category, which was burns, scalds and explosions. Since mechanical suffocation affects infants almost exclusively, it is surprising that it ranks third, with poisons other than gas, poisonous gas and firearms next in order of frequency.¹

Home accidents as a problem of community health have had minor attention in an analysis of cause, when cause is interpreted epidemiologically according to three principal factors. These are the direct etiologic agent, such as the micro-organism in a communicable disease or the loose floor board in a home accident, the characteristics of the host who develops the disease or suffers the accident, and the environment in which the host and the agent exist.⁷

Much is known about age as a determining host factor. Deaths are most frequent among infants and the aged, not only because they spend most of their time in the home but also because they are least able to guard against an unfavorable environment. In 1946, 70 per cent of all fatal accidents in children under five were home accidents. Rates for infants were three or four times those for older pre-school children. Essentially two thirds of all fatal accidents that affected persons over sixty-five years of age in 1947 were home accidents, the rates being 185.0 as contrasted to 42.4 for children under five.¹ As suggested by Britten et al.,¹⁴ it may be misleading to judge the actual incidence of home accidents on the basis of death or serious disability, because an accident with serious consequences in an aged person may be of little moment for a young adult.

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morbidity are when and where accidents occur, how they occur and to whom the accident happens. This includes a study of the site of the accident, the behavior and characteristics of the person affected, his activities at the time of the accident and, finally, the specific agent causing the accident.

Blanket-control measures have proved unproductive and expensive in any public-health program. What is needed is sufficient knowledge of the occurrence of the disease in a given community to permit a specific attack on the principal problems presented and on the most accessible link in the chain of causation. To date, not only is knowledge of the circumstances of home accidents for the country as a whole insufficient but also the available data are too often collected indiscriminately and tabulated without definite epidemiologic objectives. An evaluation of the home-accident problem, based on deaths alone, results in a distorted view of the situation.

Since home accidents vary markedly from community to community, and since few regions have adequate knowledge of nonfatal home accidents, or of the circumstances surrounding fatal mishaps, we believe that a town or county can, to advantage, study its own home accidents as the first requisite to an efficient control program. Similarly, a state control program should be preceded by representative studies of the population with samples drawn from rural, industrial, suburban, village and town areas. The kind of accident study will depend on the method selected for finding cases, and upon the finances and personnel available. The survey may be one or a combination of the following:

Study of accidental deaths in the community. An analysis of deaths resulting from accidents, without subsequent study of accidents of less serious consequence, omits the bulk of accidents in the community. As a preliminary, such a study may be valuable, particularly if a complete, individual analysis of the circumstances of each death is made. Such studies of fatal accidents in Kansas over prolonged periods have added materially to knowledge of accident etiology.

Study of home-accident cases admitted to hospitals. Most of the more serious home accidents may be assessed by a continuing study of admissions to hospitals within the area. Hospital records alone are usually insufficient to supply the necessary epidemiologic data, but can be enlarged by an accident history obtained from the patient or a member of his family, a study of the site of the accident and the co-operation of the attending physician.

Organized survey in selected areas. The most satisfactory epidemiologic data are obtained by household-to-house survey, using trained investigators and a sufficiently large sample of the population to ensure statistical accuracy. It appears purposeless to study accidents with a disability of less than one day, if the index is a disability as long as a week, many

socially and economically important accidents will be missed, especially among children and young adults. Therefore, a disability extending beyond the day the accident occurred is a reasonable inclusion index. The obvious disadvantage of the organized survey is cost, which for many communities is prohibitive.

Incorporation of the accident study into the routine activities of the health department. This is a reasonable compromise. If the health department is making other continuing surveys, the accident study may be included, using the same personnel entering the home for the original study. What is even more practical, the public-health nurse may inquire about the circumstances of home accidents as a part of visits for other purposes. Such studies are now under way in two suburban towns in Massachusetts, and a third has been started by the health department of a large industrial community. In each region, the nurses of voluntary agencies and of the health department co-operate in investigating and recording accidents occurring on home premises within the preceding thirty days.

A convenient record form provides the necessary epidemiologic data for developing a specific educational program. The household roster, often already in the nurses' record, is used as a base in the calculation of hours of exposure. Persons other than nurses may aid in such studies, but we have no experience as yet to indicate how necessary trained personnel and professional qualifications may be in the success of the survey.

The ultimate control program, as described by Brightman¹⁷ for New York State and by the Subcommittee on Accident Prevention of the American Public Health Association,¹⁸ will center around education, especially directed to groups of people who have the most accidents. It will include continuing epidemiologic studies, case finding and the treatment of the accident prone, especially children. Administratively, experience must be accumulated on what constitutes a feasible control program, and on the means for evaluating the success of a program.

SUMMARY

The interest in accidents engendered by the modern motor car and long fostered by industry has, in recent years, been extended to the other and numerically more important accidents that occur in the home. There is need for greater appreciation of the costs of accidents and realization of the fact that they can be prevented. The obligation of the moment is to co-ordinate the activities of multiple voluntary and official community agencies into an effective home-accident control program. Its success depends on the same analytic and scientific methods by which all community health problems are approached: the epidemiologic survey.

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THE NEEDS FOR INPATIENT CARE AND TREATMENT OF MENTALLY ILL CHILDREN IN THE COMMONWEALTH OF MASSACHUSETTS

THADDEUS P. KRUSH, M.D.*

WALTHAM, MASSACHUSETTS

IN PSYCHIATRY in the past thirty years there has been a gradual increasing interest in progressing downward along the chronologic scale toward childhood to seek out the earlier phases of personality deviations. To search for a means of straightening the bent twig while it is still in the process of bending appears all too obvious, but the surprising feature is the fact that it has taken so long to turn attention in this general direction. That the "hopeful" aspect of psychiatry exists in child psychiatry should be reasonably apparent to anyone who has spent long hours in individual or group therapy with mentally ill adults in an attempt to delve backward into their repressed conflicts or to enable them to obtain sufficient insight to be able to accept and deal with their environmental stresses of the moment. These patients have been chronically ill by the time that clear-cut psychotic or psychoneurotic adaptations appear.

Except in extreme deviations, the child exhibits no such well defined clinical syndromes, but the need for closer observation and classification is here necessary if the developing dynamisms of adult mental illness are to be better appreciated.

Although child guidance has done much to add to knowledge in this respect, there also appears to be a need for inpatient care and treatment of mentally ill children, particularly those exhibiting problems centered around marked withdrawal, running away, extreme aggressiveness and hyperactive-distractable types of behavior. The first named need hospitalization to be afforded a permissive, noncompetitive haven, the second need

to be maintained in a therapeutic situation for a sufficient length of time to form a relation with the therapist and more adequately to test reality, the third need some environment to contain aggressiveness until they become more aware of the source of their hostility, for they certainly do not become more secure nor is their antagonism abated by a continual shuffling of foster homes, the fourth need investigation of the central nervous system for diffuse neurologic defects and a mobilization of intellectual assets in a nonfrustrating environment. All need a multidiscipline approach to their personality disabilities to assure as rapid rehabilitation to society as possible.

In December, 1945, the Metropolitan State Hospital was designated by the Massachusetts Department of Mental Health as the institution to which all psychotic children in the Commonwealth were to be sent. During this and the following months, such psychotic children as were scattered throughout the Department's institutions were transferred to this hospital, which then began to receive severe behavioral deviants from the community. Two 50-bed wards were taken from existing overcrowded adult facilities to house the increasing influx of children. A critical evaluation of the inpatient mental facilities for children in the state is in order so that reasonable short-term and long-term goals can be established to achieve care and treatment of this group of the population.

In Massachusetts approximately 23,000 adults are at present patients in state mental hospitals. If the seed of mental illness is planted during childhood, to come to full fruition in adulthood, it seems likely that more than half of 1 per cent of the

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present capacity of institutions should be set aside for the study, care and treatment of children's mental disorders. The present admission rate of approximately 300 per year tends to confirm the need for this type of hospitalization.

Some alteration of the scope and purpose of this unit, originally conceived as one to which psychotic children could be sent for care and treatment, has been necessary, owing to the following circumstances: the prevailing types of commitment procedures, the existing confusion regarding what constitutes psychosis in childhood and the community needs for the mentally ill child.

At present a patient may be committed to the Children's Unit under Section 79, 77, 51, 100, 86 or 86A of Chapter 123 of the *General Laws*. With the exception of Sections 86 and 86A no refusal of admission exists, hence, practically all children sent to the unit are admitted, physical facilities notwithstanding. Although this is moderately frustrating to the personnel involved in the diagnosis, care and treatment of these children such procedures serve the useful purpose of funneling all patients under the age of sixteen considered by the Commonwealth to be mentally ill.

Even the most cursory examination of the field of child psychiatry reveals the fact that the diagnosis "psychosis" as applied to a childhood behavioral deviation is an ill defined entity, subject largely to the individual or staff interpretation of the moment. Considerable complication arises because of the wide range of "normal" necessitated by the uneven rates of physical, intellectual and emotional progress in the child. Here, too, one would expect to see mental illness in its nascent state rather than in the better defined chronic states as seen in adults. It appears more reasonable to accept such behavioral deviants who have demonstrated an incapacity to adjust themselves satisfactorily in an outside environment. Children with severe behavior disorders, not classifiable as psychotic but demonstrating prolonged and continuous maladjustment, would then be eligible for more protracted treatment than that given during the thirty-day observation period. As long as the emphasis on treatment and rehabilitation to society is stressed, no child will be unjustly incarcerated for an excessive period.

The existing physical facilities, largely located in the medical and surgical building of the Metropolitan State Hospital, consist of two 53-bed wards, the overflow from the boys' ward being housed on the male admission ward, a small solarium utilized for group psychotherapy, two small rooms used as classrooms, a basement playroom, two playgrounds located between the medical and surgical wings, tennis courts, bowling alleys and a gymnasium, the last three being shared with the adult patients. A five-room suite located between the wards contains an examining room, psychologic testing room,

doctor's office and two small recreational-therapy rooms.

The most urgent physical need centers around the 50-bed wards, which, originally designed for tractable adult patients, have proved too large to be manageable with 50 patients of great destructive capabilities. Obviously, a situation close to chaos would result if one admitted to the ward the most marked behavioral deviants from the following sources: Fernald State School, New England Home for Little Wanderers, Court cases pending disposition, Monson State Hospital, Lyman School for Boys, Shirley Industrial School and severely regressed and withdrawn children from the community. Only the simplest form of segregation into three groups can be effectively maintained.

These basic groups are a "deteriorated" group, the members of which need total custodial care, feeding, bathing, toileting, clothing and so forth, a "middle" group, whose members, although able to care for their own immediate physical needs, are in need of constant supervision, training and guidance, and a "self-sufficient" group capable of meeting the demands of hospital environment — that is, of assisting in ward housekeeping, kitchen duties and so forth. Such a system is at present in effect.

Adequate segregation and classification are practically impossible under such circumstances, and treatment is seriously handicapped, since carefully fostered relations between personnel and patients must frequently be strained by administrative expediency.

It is proposed that any specially constructed children's unit be composed of small family-size wards consisting of not more than 10 beds to each ward. On the basis of the present admission rate, which is still increasing, it seems reasonable to expect that approximately fifty such wards would begin to meet the needs expressed by schools, courts and community. An initial nucleus of fifteen such wards is immediately necessary, additional wards being added in a definite building program designed to fit the unit to its average patient load over a period of five to ten years. Durability, safety, ease of maintenance and access, rather than beauty of design, are prime considerations.

The most acute need of this unit is at present for personnel. A subminimal nucleus of interested, enthusiastic and somewhat frustrated persons consists of 2 doctors, a nurse, a social worker, a psychologist, a recreational therapist, and a clerk, with positions for occupational therapist and an additional nurse remaining unfilled. No provision for a separate group of attendants especially trained for work with children exists. The 13 attendants now serving on these two wards are "borrowed" from the attendants allotted the hospital for the care of adult patients.

A more detailed study of the medical needs of such a unit reveals that the physicians occupying

the positions of clinical director and assistant physician work up approximately 400 cases each year (more than 300 inpatients in addition to outpatients, chiefly committed by the courts for appraisals). Study of each inpatient consists of a social history, physical examination, laboratory examination, including an electroencephalogram, and psychiatric examination. In addition, the care of 100 regularly committed patients is administered by these 2 men. No pediatric consultant other than the regular medical and surgical consultants of the hospital is available. No formal outpatient linkage with the community is provided, though if the accent is to be on treatment and resocialization of patients, such an association is vital. Furthermore, the patients passing through and being retained in this unit represent a potential mine of information regarding early and late behavioral deviations. Proper collection and assortment of the mass of data necessary for careful study require a larger force than the bare minimum of 1 psychiatrist to 200 patients.

A proposed minimal medical staff should consist of a director, a senior physician, a consulting pediatrician, 2 assistant physicians, 2 residents in psychiatry and 4 fellows drawn from the fields of psychiatry, pediatrics and anthropology. The need for a director of such a unit is apparent. His duties should consist of co-ordinating the therapeutic and investigational work to maintain maximal efficiency with the personnel at hand. He should be responsible for decisions regarding policy and for the concerted efforts of his staff in an effort to educate the community regarding the needs of the mentally ill child. The efforts of the senior physician should be utilized in the direction of an outpatient department designed to provide the necessary community linkage, follow-up study and continued treatment of patients well enough to function on an outpatient level. Assistant physicians should be available in the ratio of 1 to every 5 10-bed wards, or 1 for each of the present 2 wards to meet the immediate needs of their wards, to carry out individual and group psychotherapy and to work on investigational approaches designed to enhance the understanding and therapy of mentally ill children. Two residents would provide training for a psychiatrist, six months each, on male and female services. An opportunity to provide shorter term training to supplement the other training programs could be met by a fellowship rotation with pediatric-psychiatric facilities maintained by general or pediatric hospitals. Such three-month indoctrination periods would provide a larger group of physicians with a better understanding of the problems confronting the mentally ill child. Judging from the large number of obvious deviations of growth in this group there seems to be a fertile field for an anthropologist to study at this level.

Since the present two-ward system obtains, the nursing problem has been estimated on this basis

Provision has been made for 2 registered nurses to provide the nursing care for the unit. This allows for coverage of each ward by nurses for forty hours a week, or less than a quarter time coverage by such personnel.

The degeneration of ward administration and treatment during the absence of nurses on the ward is all too painfully apparent, particularly on the boys' ward, where a woman's forbearance and restraining hand are sorely needed to modify the fluctuating disciplinary extremes of male attendants. With twenty-four-hour nursing care, it would not be necessary to transfer the child to the adult medical and surgical wards for treatment of accidents and illnesses not requiring isolation. It is estimated that 8 graduate nurses could provide such coverage for the present two wards. Two supervisors would be necessary to co-ordinate the unit's nursing activities. With such a staff augmented by 6 graduate student nurses obtained from a university nursing school, in addition to 4 student nurses affiliating at this hospital, such procedures as hydrotherapy and insulin therapy could be provided. At present, 4 student nurses on affiliation to the hospital gain valuable experience in mental illness only so long as a registered nurse is on duty. Their training is augmented by a two-hour clinic each week in which an attempt at altering their attitudes from apathy or hostility to acceptance of the problems presented by the patient is made. It is realized that the numbers of nurses suggested above are not available in the present-day shortage of nursing personnel so that immediate interim nursing needs should be aimed at obtaining at least 1 supervisor, 4 registered nurses, 2 graduate students and 4 student nurses to provide minimal coverage.

An additional phase of the nursing problem has to do with the attendant personnel, at present consisting of 13 assorted persons varying from those who are sincerely interested in the welfare of the patients whom they attend to representatives of the economic, social and moral fringe of society, who are attracted only by the possibility of drawing a pay check every Thursday. The present-day labor shortage and low income obtainable in this field place the accent on the latter situation, with the result that this group is highly unstable.

This fact has been demonstrated on several occasions during the process of carrying on group therapy with the patients. Basic insecurities of the attendants are activated, necessitating some group therapy of the attendants themselves. It is unfortunate that the most unstable group is numerically the largest one utilized in patient care and the group constantly in contact with the patients. More complete nursing coverage as suggested, coupled with a practical teaching program carried out by the physicians, would go a long way toward stabilizing such a group.

Social-service coverage at present is provided by the head of the department, a staff worker and 2 students. On the basis of a recent report,¹ the present inpatient and intake load will require a supervisor and 6 staff workers, in addition to the present head of the department. Augmentation of the force dealing with the manifold social problems inherent in mental illness could be accomplished by assignment of a psychiatric-social-work student to each staff worker, the supervisor acting as case consultant for these workers. Valuable insights into patient's problems are at present provided the social-service department by utilization of members of this force in group-therapy situations. Pending the achievement of the goals mentioned above, the head worker should have at least 3 staff members supplemented by three students assigned to the Children's Unit.

In the field of psychologic testing there is available at present the position of a psychologist. It is estimated that 2 psychologists are needed to cope with the present patient traffic.^{2, 3} With the addition of 2 student psychologists the necessary "battery" testing of the patients would be accomplished in a fashion designed to accumulate and analyze data in this field as an aid in more accurate classification and treatment.

From the standpoint of education, provision at present is made for the position of a teacher—1 teacher for 125 of the most disturbed "pupils" in the Commonwealth. There is a singular educational apathy toward the teaching problem posed by the unit, even though it seems apparent that here exists "exceptional" child material that should provide a real proving ground for educational methodology. The transference of results obtained with such children should prove valuable in reorienting the educational approach toward the "fringe" children of the regular and special classroom. To cite a possible example of investigation, the relation of reading disability to early primary behavior disorders should prove a fruitful source of endeavor.

Furthermore, work in this field should be supervised by competent investigators, preferably from a university graduate school of education. It is unlikely that the psychiatrist's life span will be long enough for him to master the fields of medicine, education, sociology and penology in all their details. Hence, it is not reasonable of the Department of Education to step aside on the plea that provision for such a specialized staff should be made through the Department of Mental Health. Although physicians have been exposed to lengthy educations, this in turn does not make them educators, and it seems wiser for these two disciplines to act in concert rather than to attempt to wash their hands of the matter. The least that should be done by the Department of Education is to appoint an advisory board for such a specialized educational problem.

It is estimated that a minimal educational staff should consist of a head teacher and 4 staff members, each of whom could augment his teachings by supervising a graduate student in education for each 100 patients, roughly comprising 50 per cent of patients of normal intelligence, 25 per cent of educable mental deficient and 25 per cent of custodial mental deficient. This estimate is probably inadequate and is subject to revision as better understanding of the educational problems becomes apparent to the psychiatrist.

Aside from these academic aspects, it would be advisable to provide social and vocational training. To a slight degree in small group situations, progress in the social field is at present being made. This entails the use of social workers who eat at least one meal a week with the children. Further attempts at acquiring some proficiency in household duties is afforded in another group setting off the ward. At present, no form of vocational therapy exists owing to the lack of facilities. With the exception of the last named, no new personnel would be necessary, provided a plan for training of ward personnel, including social integration as part of their duties, was made.

Provision is made for an occupational therapist, but at present such a position remains vacant. At least 2 occupational therapists should be assigned to the unit as an initial effort. One of these should be qualified to serve as a co-ordinator of play therapy and psychodramatic technics, and the other should utilize manual-training skills in a small group setting.

At present a recreational therapist is carrying a great deal of the load of play therapy in a group setting (party projects, roller skating, tennis, bowling, sledding and so forth). For the purpose of group control some supplementation of personnel is made available through attendants and student nurses at a resultant sacrifice in efficiency of ward administration. At least 2 counselor assistants, possibly drawn from the field of group work of a school of social work, are needed, particularly from the standpoint of the juvenile delinquent who comes to the unit for a period of observation.

As a supplement to occupational and recreational therapy, community group activities designed to provide a link with society when the child is returned to the community are established, but are as yet functioning poorly. Boy Scout and Girl Scout activities of this sort are attempts at providing such a transition.

In the realm of motion pictures, the productions have been largely recreational, but more recently use has been made of educational films as well. This could be greatly supplemented by membership of the unit in a university educational film library for the purpose of obtaining visual teaching aids.

Although religious education of these children should be neither rigidly directive nor compulsory,

it should be available to the degree that would meet each child's religious need. The Catholic clergy, and to a lesser degree, a Protestant minister, are at present attempting, within the confines of their respective religions, to meet this need. It seems advisable, in view of the lack of moral concept apparent in some patients, that such education should be made available without coercion. An inter-faith advisory board composed of interested clergy could best indicate how this might be carried out in an institutional setting.

From the legal standpoint, such a unit as this becomes increasingly important, directly as the judiciary and law-enforcement agencies recognize the fact that punishment does not always fit the crime. It is not our intent to pamper persons who have clearly demonstrated antisocial tendencies, particularly if the offenses are aggressive and capable of inflicting injury on others, but the apparently prevalent view that "what they need is a good lashing" is not subscribed to, firstly because many of these patients are almost literally driven to their expression of antisocial behavior by such a social attitude so far as can at present be observed, and secondly because the motivation of antisocial behavior should be studied for the valuable insights that will be necessary for its control and prevention. Such insights will not be forthcoming by the use of coercive measures. Particularly is this true in the field of sexual deviation, in which the sensibilities of many people seem to be so sorely offended, judging by the resultant hue and cry when the public is afforded the opportunity of harrying one of these unfortunate persons into a prison.

Provision for the juvenile delinquent in this unit is predicated on the belief that he represents a sufficiently aberrant behavioral pattern to be classified as mentally ill—hence, the need for observation and treatment rather than custodial care. This is not intended as an argument for the emptying of prisons into the mental hospitals, but rather as a plea for extension of psychiatric facilities to the penologic system. A unit such as this can serve largely for classification, aiding in the more complete evaluation of the social offender and as a treatment unit for selected research problems in this field. At present well over 50 per cent of admissions are at the behest of law-enforcement agencies, and it appears that some steps in the correct direction are in the process of being taken by the Youth Service Board.

The clerical needs of the unit cannot in actual practice be met by one clerk, as is provided in the present table of organization, so that at present this position is pooled with the clerical help of the rest of the hospital to obtain an even apportionment of the work to the available clerks. In this fashion, the minimal needs are at present met, with some consequent sacrifice of the clerical efficiency of the rest of the hospital. It appears that at least 3 clerks are necessary to accomplish the present unit record work, particularly in view of the fact that a greater portion of the outpatient work is at present done in penciled notes. With some semblance of adequacy in this department, the records and clerical personnel should then be moved closer to the actual patients, the information previously obtained by the personnel being thus more readily available for the purpose of treatment and research.

The present medical administrative routine is that the superintendent and the assistant superintendent deal with the problems of housing, clothing, feeding and medical supply, attempting to meet the increasing needs of the unit through the regular hospital budget. Since the budget is planned at least a year in advance, the expanding needs of the unit can never be met even minimally. Until a more realistic attitude is taken regarding the expanding budgetary needs, the unit must continue to be society's orphan, begging for its very existence.

From the economic standpoint in the operation of a unit such as this, the experience garnered in the past three years indicates that the Commonwealth has been functioning in a manner similar to that attributed to "Peter at the Dike," stuffing his arm into the leak in the dike to prevent its being washed away completely. The continual destruction and repair necessitated by the large unmanageable wards falls into such a category.

From the standpoint of adequately serving the Commonwealth, it is necessary that a departure from the present available setup be made, preferably along the lines indicated above. It is realized that the initial expenditure would be considerably more than that at present being dribbled away in a year's time. However, over a longer period, it is apparent that a well integrated unit, designed to meet the needs expressed by the Commonwealth, would be more efficient and less costly than the present attempt at patching inadequate facilities.

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3. *Ibid*. Report No. 5. April 1948.

A PUBLIC-HEALTH HEART PROGRAM — FIRST REPORT*

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BOSTON

IN MAY, 1948, the Massachusetts Medical Society endorsed in principle a pilot study of the public-health aspects of heart disease.¹ The study was to be conducted in Newton under the joint sponsorship of the Newton Health Department, the Massachusetts Department of Public Health and the United States Public Health Service.² Its objectives were to determine methods of helping to reduce cardiovascular disease and conserve cardiac function.

A period of a year does not allow sufficient time to draw definite conclusions or submit findings for qualitative or quantitative analysis. However, it does seem fitting to report to the Massachusetts Medical Society concerning the activities that have been initiated and to indicate the direction of the program.

The Newton Heart Demonstration Program, as the pilot study has since become known, is a frankly experimental venture. It rests largely on a belief — held by many cardiologists and public-health authorities — that heart disease constitutes a public-health problem.³ Mortality statistics show that deaths from diseases of the heart exceed those from any other cause.⁴ Many other criteria usually considered before establishing public-health programs remain undetermined when applied to heart disease. For example, how many people in a community are actually ill of heart disease? What is the age at which they are affected? To what extent can heart disease be prevented? How much salvage can be effected for those in whom the disease in one of its forms develops? What aspects of the problem cannot be met except by community measures? And what is the cost of these measures? Finally, what evidence is there that public-health measures will yield results?

Many heart studies will probably be needed to provide answers to these questions. But the United States Public Health Service initiated a local study in an attempt to determine the value of organized community action in helping to meet cardiac needs, and the costs and effectiveness of such action.

The Massachusetts Department of Public Health was asked to co-operate. The Commissioner obtained the assistance of the Committee on Public

Health of the Massachusetts Medical Society. Also, the Commissioner appointed a technical advisory committee of leading cardiologists and public-health authorities.

It was believed desirable to conduct the study in a community that employed a full-time, trained medical health officer and furnished basic public-health services. Several communities were surveyed. Newton was selected, and a unit of public-health-service personnel, previously assigned to the Commissioner, was reassigned to the Newton Director of Public Health.

The co-operation and leadership of the Newton medical profession were considered essential. The practicing physician represents the greatest potential source of knowledge of the cardiac problem in the community. With him rests responsibility for diagnosis and treatment of the patient with heart disease. Supplementary services may contribute to the patient's welfare, but they can only be utilized under the supervision of the physician. The key place that the practicing physician naturally occupies was therefore the major consideration in the plans for the heart program.

When the demonstration had become established in the health department, the Director of Public Health and the Medical Officer of the unit requested the assistance of the Newton Medical Club. The President assigned the Committee on Public Health to work with the health department to explore program possibilities and develop preliminary plans. At the request and under the supervision of the Committee, a small survey of the cardiac patients of private physicians was made. The survey, although not statistically significant, yielded information concerning the extent to which existing facilities for cardiac patients were being used, and indicated some of the social and public-health problems of heart disease. On the basis of the findings, a tentative outline of activities for the Heart Demonstration Program was drawn up and presented to the Newton Medical Club, which, in October, 1948, gave its unanimous endorsement.

Medical guidance for the Newton Heart Demonstration Program today lies with a group of 6 physicians known as the Cardiac Program Committee. This committee was appointed by the president of the Medical Staff of the Newton-Wellesley Hospital. Members include 5 internists, 3 with special interest in heart disease, and a pathologist.

*Presented at the annual meeting of the Massachusetts Medical Society, Worcester, May 24, 1949.

†Chairman, Cardiac Program Committee, Newton Heart Demonstration Program.

‡Commissioner, Massachusetts Department of Public Health.

§Director of public health, Newton Health Department.

¶Chief, Division of Cancer and Other Chronic Diseases, Massachusetts Department of Public Health.

||Medical officer in charge, Heart Demonstration Programs, United States Public Health Service.

The functions of this committee are to furnish technical leadership and share jointly with the health department in planning the heart program. The Director of Public Health and the Medical Officer of the program meet with the committee once a month or more. The first meeting was held on December 3, 1948.

FIRST FIVE STEPS

After several months of study, a five-point program was recommended for early action. It called, first, for a well informed medical profession, since any services made available to the cardiac patient would be given either by the physician or under his supervision. Secondly, information on the amount and kinds of heart disease occurring in Newton was needed to permit more intelligent program planning. Thirdly, the participation of the public was desired to ensure full use of community resources. Fourthly, a study of the dietary needs of cardiac patients appeared necessary since nutrition touches upon many aspects of prevention and treatment. And, finally, the rehabilitation needs of the patient required investigation if he was to receive full benefit from medical treatment.

Subcommittees were established for the further study and development of the five steps. They included physician education, temporary voluntary reporting, community organization, nutrition and rehabilitation. A sixth subcommittee was set up to consider additional program possibilities.

Subcommittee on Physician Education

The goal of the subcommittee on Physician Education is to contribute to the improvement of diagnosis and treatment of heart patients in Newton. Knowledge of heart disease is advancing rapidly. Every additional development offers new hope and carries with it responsibility for improving the care of the cardiac patient. To help Newton physicians keep abreast of the developments the Cardiac Program Committee is sponsoring monthly discussions of modern cardiology known as the Newton Postgraduate Heart Institute. A serious attempt is being made to keep the discussions practical and to foster audience participation. Content is based on interests and needs of local physicians as indicated by a preliminary questionnaire and the expressed wishes of those attending the meetings. The first two sessions included talks on "Practical Aspects of Heart Disease" and "Prevention of Heart Disease." The third meeting will be a discussion entitled "Cardiac Emergencies."

Subcommittee on Temporary Voluntary Reporting

At an early date, the Cardiac Program Committee felt the need for an inventory of the cardiac problem in Newton. The vital statistics of the health department and the hospital records have been studied in an attempt to determine the amount

of heart disease in the community and the relative importance of the various types. However, it was believed that information more pertinent to program planning might be obtained if private physicians were to report cardiac cases.

To test the value of such a procedure, for a three-month period the members of the Cardiac Program Committee and the subcommittee are reporting their cardiac cases to the health department. Besides data concerning the disease the reporting form is designed to indicate the extent of the need for such supplementary services as nutrition and rehabilitation.

Subcommittee on Community Organization

As in all public-health projects success of the Newton Heart Program will depend to a great extent upon support by the public. An interested well informed citizenry is not enough. They should actually participate by helping to implement some of the nonmedical aspects of the program.

Plans are being studied for developing an organization representing all interested agencies, clubs and people of Newton. As a first step in this direction an inservice education program has been carried on for community health and welfare personnel. The Heart Demonstration Program has twice conducted a course in "The Public Health Aspect of Heart Disease" to help these workers become more familiar with cardiac problems. Members of the Cardiac Program Committee, as well as Boston cardiologists and public-health leaders have appeared as speakers.

Subcommittee on Nutrition

The importance of special diets in the treatment of heart disease⁵ suggested possibilities for a community nutrition program. A small study has been started to determine methods of approach and consider the problems involved.

Instruction is being given by the nutritionist of the demonstration unit under the supervision of the attending physician. Patients referred for reduction, low-sodium and rice diets are included.

From a careful appraisal of the results of this study, it is hoped to develop procedures for providing some part of this service through group meetings, public-health nurses and other available community resources.

Subcommittee on Rehabilitation

The Cardiac Program Committee believed that rehabilitation represented one of the most challenging fields for action. Providing diversional activities during the period of convalescence, helping the patient resume his duties in the home and, perhaps most important, assisting him to return to a productive job will contribute to his mental well being and, therefore, to recovery. Certainly in this phase of the program, widest use will be made of exist-

ing community agencies and of such state agencies as the Department of Vocational Rehabilitation. The Subcommittee on Rehabilitation has recommended the addition of a trained worker to the staff of the demonstration unit to assist in developing the possibilities of this program. Action has been delayed pending his arrival.

The activities undertaken so far are regarded only as a beginning. They represent some of the more obvious needs that must be met to improve the status of the cardiac and the potential cardiac patient. Frankly experimental, they may be changed and adjusted with time and experience.

FUTURE PLANS FOR THE PROGRAM

Additional problems of cardiac patients are being studied. Programs for prevention, for medical salvage and for case finding are under consideration.

Prevention

Prevention offers the greatest hope. By prevention we mean measures taken to delay heart disease and prevent complications. The Cardiac Program Committee is especially concerned with the need for a weight-control program, prophylaxis of subacute bacterial endocarditis and prophylaxis of rheumatic fever.

Weight Control

Obesity after middle age shortens life expectancy.⁶ The Subcommittee on Nutrition is concerned with the part excessive weight plays in the causation of heart disease, and has given a weight-control program a high priority in its plans. However, the Subcommittee has a profound respect for the difficulties of achieving results by public-health methods. The problem is threefold: the prevention of obesity, reduction of those who are overweight and maintenance of ideal weight after reduction. The problem of weight control is almost as difficult as that of keeping an alcoholic patient sober. In fact, the technics of Alcoholics Anonymous are being studied to determine if any are applicable to control of obesity.

Since there are many dangers of obesity and the person seeking to lose weight may be sick, medical supervision will be an important part of a weight-control program.

Subacute Bacterial Endocarditis

Although subacute bacterial endocarditis accounts for a relatively small percentage of cardiac cases, its importance from a public-health standpoint is enhanced now that it can be successfully treated and apparently even prevented.⁷ Prevention often depends on the use of prophylactic drugs for all patients with valvular and congenital heart disease undergoing any oral operative procedure and even dental prophylaxis. The Cardiac Program Committee and the Newton Dental Society are

therefore planning a co-operative study of the problem. A joint committee has been established to recommend methods by which physicians and dentists of Newton can help prevent subacute bacterial endocarditis.

Rheumatic Fever

Prevention of recurrences of rheumatic fever during the months of hemolytic-streptococcus infection has been placed on the agenda for future study. The Committee plans to determine the extent to which prophylaxis of rheumatic fever is used and would also like to determine to what extent school physicians are aiding in case finding of rheumatic fever. It is hoped that, in attempts to make preventive measures available, not only encouragement but also active support can be given to public agencies and private physicians responsible for children who have had rheumatic fever.⁸

Medical Salvage

Our future program must also consider facilities in the community for meeting unsolved problems in diagnosis and treatment. The committee hopes to help develop and extend resources that can aid the physician in diagnosis and treatment. These include, among others, the cardiac clinic and agencies doing public-health nursing and medical social work.

Cardiac clinic The cardiac clinic, operated by the outpatient department of the hospital, can be one of the most effective aids of a community heart program. Standards for cardiac clinics have been developed by the New York Heart Association and adopted by the American Heart Association. It is the belief of the association that the cardiac clinic should serve as a center for physician education, and as a clinic for the diagnosis and treatment of indigent persons. The committee hopes to help develop and strengthen the local cardiac clinic to carry out the functions recommended by the American Heart Association.

Public-health nursing As the activities of the heart program become more numerous, there will be greater dependence upon the work of the public-health nurse. She can play a significant role by rendering bedside nursing care in the home, by referring potential cardiac cases for diagnosis, by interpreting, at the physician's request, diagnosis and treatment, by following lapsed cases for referral back to physicians or clinic, and by directing patients to community agencies for needed services.

Two nurses, with special training in heart disease, have been included in the demonstration unit. They will help the general staff nurses of the health department and the District Nursing Association to develop an awareness of the cardiac problem.

Medical social work Medical social activities of the hospital, clinic or welfare agency, carried on

under the advice and guidance of physicians, can be of help to cardiac patients in every stage of their illness. The availability of case-work services to patient and family may help to eliminate many of the hazards of long-term illness. Such a service will be encouraged as the Newton Heart Program begins to develop its activities further.

Case Finding

Since there is a growing optimism about the results to be obtained through early treatment of heart disease, one of the chief concerns of the Cardiac Program Committee is to get possible cardiac patients to their physicians for early diagnosis. One answer, of course, is to encourage periodic physical examinations by physicians, and this will be done. But it is often difficult to persuade people to see their physicians so long as they are well, and many physicians find that the time available for periodic examination of healthy people is limited by the demands of those who are ill.

Solution of the problem may be found in a screening method that will permit the examination of well people and the referral of suspected cases to their private physicians. Possibilities are being studied by a subcommittee.

Individuals vary in their likelihood for developing heart disease. It has been shown⁹ that, when neither parent has hypertension, only 3 per cent of the offspring of such parents were found to be hypertensive. However, when both parents were so affected, 45 per cent of the offspring were found with hypertension. There are similar leads in rheumatic heart disease and coronary-artery disease.

Perhaps the people who are most likely to develop heart disease should be shown that they require more frequent checkups from their physicians. We are studying the possibility of devising a chart to show each person the extent of his heart hazards. In this way, our limited resources for case finding may be directed where they are most needed.

Many of the plans of the Newton Heart Program are based upon recent developments in the field of

cardiology. It can safely be said that a program of this sort is possible today only because of these new developments. However, many more measures are needed before a significant reduction in heart disease in the productive ages can be achieved. We look to the research field to provide us with the tools.

If the medical and public-health professions have a program in operation that can effectively apply preventive and salvage measures as they are unearthed, the time lag between laboratory discoveries and protection and healing can be reduced.

SUMMARY

An interim report of the Newton Heart Demonstration Program is presented.

The aims of this program are to analyze the extent of the heart-disease problem in a local community, to analyze the present unsatisfied needs of the potential and actual heart patient in the community, to evaluate the possible role of public-health and other local agencies in meeting these needs, to obtain total physician participation in the program and encourage ever-increasing improvement in the quality of medical care, to help develop a permanent all-out effort against the No. 1 killer of Americans.

A review of the efforts to date is presented.

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THE RELATION OF CAVITY TO THE DEVELOPMENT OF STREPTOMYCIN-RESISTANT TUBERCLE BACILLI IN PULMONARY TUBERCULOSIS*

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IT IS increasingly apparent that the usefulness of streptomycin therapy in pulmonary tuberculosis is seriously limited by the frequent and often early appearance of tubercle bacilli that are resistant† to the drug. The development of this resistance in vitro has been observed to coincide with loss of effectiveness of the drug in vivo¹⁻⁴

The incidence of streptomycin resistance has been found to increase with the number of days that treatment is given^{1, 3, 5, 7}. It is believed, in addition, that resistant strains appear earlier and more frequently in patients with severe constitutional symptoms and in those with extensive pulmonary involvement^{4, 5}. On the other hand, the development of resistance apparently bears no relation either to the size of the daily dose of the drug or to the frequency of its administration during the day⁶.

That the development of streptomycin resistance may be a serious complication is made painfully clear to the clinician who no longer has available its remarkably beneficial therapeutic effect for coincident use in resectional surgery, or for the treatment of a serious, acute pneumonic spread of disease.

The temptation to use the drug in chronic pulmonary tuberculosis, however, remains strong. This is not only because of the unpredictable and striking benefit occasionally seen but also because the tubercle bacilli of a small number of patients unaccountably fail to develop resistance even if the patients are treated for four months or more.

This study was originally suggested by the finding of a considerably lower incidence of streptomycin resistance in patients at Trudeau Sanatorium (Table 1) than in patients being treated elsewhere⁵. The difference was made more significant by the fact that the same criteria and methods for determining streptomycin resistance⁷ were used in the two series. It was further noted that streptomycin-resistant tubercle bacilli were only rarely recovered from patients who showed no roentgenographic evidence of pulmonary cavity before streptomycin treatment.

This report is a critical analysis of these data in an effort to discover whether a relation exists be-

tween cavity and the development of streptomycin resistance.

MATERIALS AND METHODS

The material for this study consists of all the 117 patients§ treated with streptomycin¶ between November, 1946, and December, 1948, from whom adequate sputum specimens|| were obtained during and after completion of streptomycin therapy. In 6 patients a second course of streptomycin given from six to eighteen months after the first course was arbitrarily considered a separate case, making 123 cases in all. The two courses given to each of these 6 patients were considered individually regarding the duration of therapy. There were only 116 cases studied, since 7 were excluded from analysis because of certain indications for use of the drug, as follows: during and after pneumonectomy, 1, tuberculous bronchiectasis, 3, and tuberculous empyema, 3.

The indications for streptomycin in the 116 cases studied were progressive pulmonary tuberculosis, 98, endobronchial tuberculosis without cavity, 14, tuberculous laryngitis, 2, and intestinal tuberculosis, 2.

All patients had active pulmonary tuberculosis, and the sputum in all 116 cases was positive before therapy. Plaingrams were widely used to determine the presence and extent of cavity. Treatment of 16 cases was begun before admission to the sanatorium. In each of the other 100 cases in which treatment was initiated at the sanatorium or at Saranac Lake, sputum cultures obtained before therapy revealed strains of tubercle bacilli that were sensitive to streptomycin. Very small numbers of tubercle bacilli, natively resistant to low dilutions of streptomycin before treatment, are disregarded for the purposes of this study.

The daily dose of streptomycin in this series varied from 0.5 to 2.0 gm per day, but was usually 1 gm per day. The drug was given in two daily intramuscular injections at twelve-hour intervals in almost every case.

The method of sputum concentration, culture and inoculation of mediums containing varying dilu-

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†Associate medical director, Trudeau Sanatorium.

‡The terms 'resistance' and 'streptomycin-resistant tubercle bacilli' in this report refer to organisms whose growth is not inhibited by 10 microgm of streptomycin or more per cubic centimeter of Tween-Albumin medium. The terms 'sensitive' and 'streptomycin sensitive tubercle bacilli' refer to organisms whose growth is inhibited by 10 microgm of streptomycin or less per cubic centimeter of Tween-Albumin medium.

§I am indebted to Drs. J. N. Hayes and H. F. Parry of Saranac Lake, New York, for permission to use clinical material on 10 of these patients who were treated with streptomycin obtained from Trudeau Sanatorium.

¶Most of the streptomycin used at Trudeau Sanatorium and in the 10 patients at Saranac Lake was obtained through a grant from the American Trudeau Society.

||Fifty-hour sputum concentrates were obtained at weekly intervals during therapy and at monthly intervals thereafter. Gastric washings were obtained if possible when no sputum was obtainable and when sputum cultures had become negative.

tions of streptomycin used in these cases has been reported in detail elsewhere ^{7*}

RESULTS

Table 1 summarizes the incidence of drug resistance that developed in the 100 cases found positive by sputum culture at some time after completion of streptomycin therapy. The number of

before therapy and were presumably due to caseous foci ("filled-in" or "potential" cavities), later discharged their contents and appeared on the roentgenogram as cavities. The third patient was quite ill with extensive chronic endobronchial disease [†]

When cavity was present and satisfactory collapse§ therapy had been initiated just prior to drug therapy, drug resistance had developed in 2 (10 per cent) of

TABLE 1 Development of Streptomycin-Resistant Tubercle Bacilli in 116 Cases at Trudeau Sanatorium

DURATION OF TREATMENT*	NO OF CASES TREATED	NEGATIVE CULTURES AFTER COMPLETION OF THERAPY	POSITIVE CULTURES AFTER COMPLETION OF THERAPY		
			TOTAL	SENSITIVE	RESISTANT
no					
1	6	0	6	4	2
1½	46	6	40	35	5
2	41	3	38	24	14
3	11	2	9	6	3
4	9	5	4	4	0
More than 4	5	0	5	2	1
Totals	116	16	100	75	25

*Approximate

cases in which resistant organisms for each of the various durations of therapy developed is shown, the numbers in each group are too small to justify the use of percentages.

In Table 2 the incidence of streptomycin resistance in 3 classes of patients is recorded.

When cavity was present before therapy and no satisfactory collapse measure was applied coincidentally, streptomycin resistance was found in 20 (40 per cent) of 51 cases with positive cultures at the end of treatment. Nine of these 20 showed organisms resistant to 1000 microgm of streptomycin per cubic centimeter of medium.

When no cavity was present before therapy, drug resistance had developed in 3 (11 per cent) of 29

20 cases with positive cultures at the end of treatment.

The highest degree of resistance attained by any of the 5 cases showing resistance in the last two groups was to 60 microgm of drug per cubic centimeter of medium.

It is of interest that in 14 cases treated primarily for endobronchial disease without cavity and having positive cultures at the end of therapy, drug resistance occurred in only 1 (7.3 per cent). The mean duration of streptomycin therapy in these 14 cases was two and seven-tenths months.

The significance of the notable differences in incidence of resistance in the three groups is open to question, since there was not only a wide varia-

TABLE 2 Relation of the Presence or Absence of Pulmonary Cavity before Therapy to the Incidence of Development of Resistance after Streptomycin

CAVITY STATUS JUST BEFORE STREPTOMYCIN THERAPY	TOTAL CASES	MEAN DURATION OF THERAPY	NEGATIVE CULTURES AFTER COMPLETION OF THERAPY	POSITIVE CULTURES AFTER COMPLETION OF THERAPY		
				TOTAL	SENSITIVE	RESISTANT
Cavity present no collapse	55	2.1	4	51	51	20 (40%)
No cavity	36	2.4	7	29	26	3 (11%)
Cavity present coincident collapse	25	1.9	5	20	18	2 (10%)
Totals	116		16	100	75	25 (25%)
Average		2.1				

cases with positive cultures at the end of treatment. In 2 of these 3, areas of large uniform heavy density on the roentgenogram, which were present

*All laboratory studies on these patients were performed at the Trudeau Laboratory under the direction of William Steenken, Jr., and Emanuel Wolinsky, M.D., to whom I am indebted for assistance and for the use of these data.

†Unsatisfactory pneumoperitoneum and pneumothorax were abandoned in 2 cases during streptomycin therapy. 1 pneumoperitoneum was continued for purely psychologic reasons but because of poor collapse of the lungs was classed as no collapse.

tion in duration of therapy in individual cases (Table 1) but also a moderate difference in the mean durations of therapy (Table 2).

The relation of incidence of resistance to duration of therapy in pulmonary tuberculosis has been de-

‡Resistant organisms were also recovered from 2 out of the 5 cases of old empyema not included in this study.

§Satisfactory collapse measures used were as follows: thoracoplasty 12 cases, pneumothorax 3 cases, pneumoperitoneum 7 cases, and pneumoperitoneum with phrenicoplasty 3 cases.

terminated by several investigators. The Veterans Administration has reported the largest experience so far.⁶ Only an insignificant difference was found in the incidence of resistance in patients treated for one hundred and twenty days with 0.5, 1.0, 1.8 or 2.0 gm per day. Table 3 summarizes their findings in 1030 patients so treated. The incidence of drug resistance in 46 patients treated at the Veterans Administration Hospital in Sunmount, New York, and determined at the Trudeau Laboratory⁷ rather closely paralleled these findings. The observations of others have been similar.²⁻⁵

Each case in the three groups of Table 2 was then assigned an individual chance of developing resistance, on the basis of the percentages in Table 3, for example, resistance is predicted in 24 per cent of those receiving treatment for one month and is

TABLE 3 *Relation of Duration of Daily Streptomycin Treatment (0.5 to 2.0 gm) to the Incidence of Development of Drug Resistance**

DURATION OF DAILY STREPTOMYCIN THERAPY mo	POSITIVE CULTURES SHOWING RESISTANT BACILLI %
1	24
1½	36
2	50
3	64
4	72
More than 4	85

*Data from Veterans Administration Hospital reports

therefore predicted in 24 out of 100, 0.24 out of 1, 0.48 out of 2 and so forth. The decimal numbers of cases of resistance predicted in each group were totaled, divided by the number in the group and then converted from a decimal back to a percentage. The chance of resistance predicted in this way on the basis of duration of therapy was found to be approximately the same for each group — 48, 49 and 42 per cent, respectively. Therefore, the difference in the actual incidences observed — 40 per cent in the first group, 11 per cent in the second and 10 per cent in the third — is considered to have a significance not materially influenced by variations in duration of therapy.

The size of cavity present before therapy also bore a numerical relation to the incidence of development of resistance in this series. Cavity was measured roughly as the total average roentgenographic diameter of all cavities in both lungs. Of 55 patients with cavity before therapy, 51 still had positive cultures after therapy. Resistance developed in 12 per cent of 8 cases with cavities of 1 cm or less, in 33 per cent of 27 cases with cavities of 1.5 to 3 cm and in 63 per cent of 16 cases with cavitation of 3.5 cm or more. The mean duration of therapy varied from two and one-tenth to two and two-tenths months in these three groups.

There were 45 cases in which cavities failed to disappear during streptomycin treatment. The tubercle

bacilli recovered in 24 of these remained drug sensitive, those in the other 21 developed resistance. Although the cases developing resistance tended to have had more extensive cavitation and more severe constitutional symptoms than those retaining sensitivity, it must be emphasized that there were certain notable exceptions.

DISCUSSION

These findings are in accord with the observations of Howlett and O'Connor,⁸ who reported that streptomycin resistance developed in only 1 of 15 patients treated for a chronic disseminated nodular type of pulmonary tuberculosis. Further experience to date⁹ supports their view that "resistance occurs more commonly in patients with frank caseation or persistent cavity."

The mechanism of streptomycin resistance is not clear. The observations in this series and those of Howlett and O'Connor suggest that the amount of caseation may have an important bearing on the phenomenon. Resistance is theoretically more likely to develop when bacilli are exposed to low concentrations of the drug. Such a low concentration could be due either to the impaired blood supply in caseous tissue or to the presence of excessive numbers of bacilli, or to both.

Streptomycin-resistant tubercle bacilli have been recovered after treatment in some cases of miliary tuberculosis^{6, 10} and tuberculous meningitis^{10, 11} in which there was no demonstrable cavitation. In these cases, however, there was usually pathological evidence of a grossly caseous focus near a blood vessel, which had presumably given rise to the dissemination.

Both sensitive and resistant organisms have been recovered at autopsy from different parts of the body and even from different foci in one lung.¹² There may therefore be justifiable doubt that the tubercle bacilli isolated from a patient at any one time are truly representative of all the organisms infecting the host. In this connection, it is also possible that collapse traps secretions containing tubercle bacilli of a state of sensitivity or resistance differing from those contained in material reaching the laboratory from other parts of the lung.

When sputum cultures become repeatedly negative before termination of drug therapy, the *in vitro* reaction to streptomycin of the tubercle bacilli still within the body is also unknown. Streptomycin-resistant tubercle bacilli have occasionally been recovered for the first time from cultures again found positive some months after turning negative.¹³ When cultures of the collected material had become repeatedly negative in 16 cases of this series, there was a coincident clinical arrest of the disease. In addition, all positive cultures obtained before sputum conversion in these 16 cases revealed sensitive organisms.

The exact level of streptomycin resistance at which a serious interference with the clinical effectiveness of the drug occurs is still not clearly established. There is no longer much doubt, however, that *in vitro* resistance to streptomycin is to be avoided at all costs, if possible. Nevertheless, at times it may be poor judgment to fail to use the drug because of this fear when there is indication for the drug and a reasonable chance of lasting benefit. This will be true without reservation when the clinician or bacteriologist is able to select the cases in which drug resistance is most unlikely to develop. This study suggests that careful selection of cases for drug therapy may significantly reduce the risk of drug resistance in chronic pulmonary tuberculosis.

Perhaps a more important, though less well documented, observation is the use of collapse measures coincident with streptomycin therapy to reduce the risk of drug resistance. Others have already suggested that streptomycin be used to prepare the patient for collapse therapy.^{13, 14} In certain situations, especially in the treatment of acute pneumonic or rapidly progressing lesions, this approach appears sound in spite of the risk of development of resistance. When pneumothorax is planned and tuberculosis of the smaller bronchi is suspected, or when bronchoscopy is not available in a suspicious case, a two-week or three-week course of streptomycin before collapse may reduce pneumothorax complications.

If the experience of others confirms the findings of this study, however, it appears logical to withhold streptomycin, whenever possible, until collapse is well established and is having a satisfactory relaxing effect on the cavity-bearing lung. This course is sound when one considers how long it often takes to establish a suitable collapse, and how quickly drug resistance sometimes supervenes. Pneumothorax may lead to one or more thoracoscopies, pneumopentoneum may require the addition of phrenicosis or vice versa, more stages of thoracoplasty may be required than originally planned, and, finally, two or more different collapse measures may have to be tried because of mechanical failure of the measure first chosen. If streptomycin is given first or coincident with the beginning of the first collapse measure employed the usual

forty-two-day to sixty-day course of the drug may well be completed and the bacilli may have become resistant before collapse is mechanically satisfactory.

With increasing knowledge of the advantages and limitations of both streptomycin and collapse in chronic cavitary pulmonary tuberculosis, it is no longer always rational to try each method separately. In the light of these observations, coincident utilization of the mechanical effects of collapse and the immunologic benefits of streptomycin should be seriously considered.

SUMMARY

In a series of 116 patients treated with streptomycin at Trudeau Sanatorium positive sputum or gastric cultures were obtained from 100 at some time after therapy was completed. In these 100 cases *in vitro* resistance to the drug developed as follows: in 40 per cent of 51 with pretreatment roentgenographic evidence of cavity and no coincident collapse, in 11 per cent of 29 without cavity before therapy, and in 10 per cent of 20 with cavity before therapy but with a coincident satisfactory collapse measure.

The possible explanation and clinical significance of these observations are discussed.

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MEDICAL PROGRESS

CHILD HEALTH SERVICES IN MASSACHUSETTS

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THE American Academy of Pediatrics has completed a nation-wide study of health services for children. The findings were published by the Commonwealth Fund in April of this year, and have already led to action to improve the health of the nation's children. The study originated in 1944 when the Committee on Post-War Planning reported to the membership of the Academy on the general situation regarding the health of the country's children and recommended that a survey of existing health services be made before any future health program was undertaken. At the same time legislation was pending in Congress that threatened radically to change the nature of medical practice. The study was to ascertain the extent and distribution of present services to children whether provided by professional men in practice, by hospitals and clinics, or by voluntary and official community health agencies.

The Academy study began in North Carolina in the fall of 1945. Other state studies were started in the spring of 1946, following procedures set by the Committee for the Study of Child Health Services, with a central office under the leadership of Dr. John P. Hubbard, the executive director. The results of these studies are now being published in most of the states and recommendations are being made regarding future action, state by state, in the light of local conditions.

This effort is striking evidence of the collective concern of the physicians and dentists of the country for the welfare of children. It is the first time that doctors have pooled their voluntary efforts and inquired into the facilities serving the nation's child population. The survey was made by those directly responsible for rendering health service, and the recommendations are based on facts viewed in the light of a knowledge of local conditions within the states.

In the development of the survey it was left to the initiative of each state chairman to develop an organization in his state, make plans for the distribution and collection of schedules, finance the work and arrange for the reporting of the findings. The central office was responsible for setting the procedures to be followed, for tabulating the data and for returning information to the states for their own use.

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The Massachusetts study corroborates and emphasizes some of the national findings of the Academy. The importance of the general practitioner in caring for children and the uneven distribution of medical services are both apparent. In Massachusetts, as in the country generally, three fourths of the private medical care of children is supplied by general practitioners. They take care of most of the sick children and also, as a group, do most of the well-child supervision.

Massachusetts, in common with most of the New England states, possesses certain characteristics that set it off from the rest of the country. The population is older. Per-capita incomes are high. There are many small and independent agencies serving children, and official health activities are administered by the local city or town rather than by the county.

MASSACHUSETTS STUDY

The Massachusetts Study of Child Health Services was organized in the spring of 1946 and its report, of which this article is a digest, has recently been published by the American Academy of Arts and Sciences ‡.

In tabulating data and for comparing sectional differences in health service the Academy study has compiled its information by county and by "metropolitan character of county." This statistical device, which classifies counties according to both population density and proximity to centers of population, is of less use in Massachusetts, where there are only fourteen counties and the population is more uniformly distributed than elsewhere. There are only three "isolated" counties in the Commonwealth: Barnstable, Dukes and Nantucket. Comparatively rural areas in several other counties are obscured (Fig. 1). For this reason Massachusetts data have also been tabulated by health districts, since these seem more adequately to bring out variations in service. Furthermore, they correspond to the present administrative areas of the Massachusetts Department of Public Health (Fig. 2).

Detailed information regarding the collection of data for the Massachusetts study will be found in the complete report to which reference has already been made.

‡American Academy of Arts and Sciences, *Health Services for Massachusetts Children*. Special publication 1949.

Massachusetts is the twelfth wealthiest state in the Union, with an average annual per capita income of \$1289, but in 1946 the Commonwealth ranked twenty-second in maternal mortality and twentieth in infant mortality among the states (Table 1) Boston its largest city, had an infant mortality one

marized report, but the salient points are briefly outlined, together with selected supporting data

Total of Medical and Dental Service for Children

Massachusetts ranks third in the country with respect to the total amount of medical service that

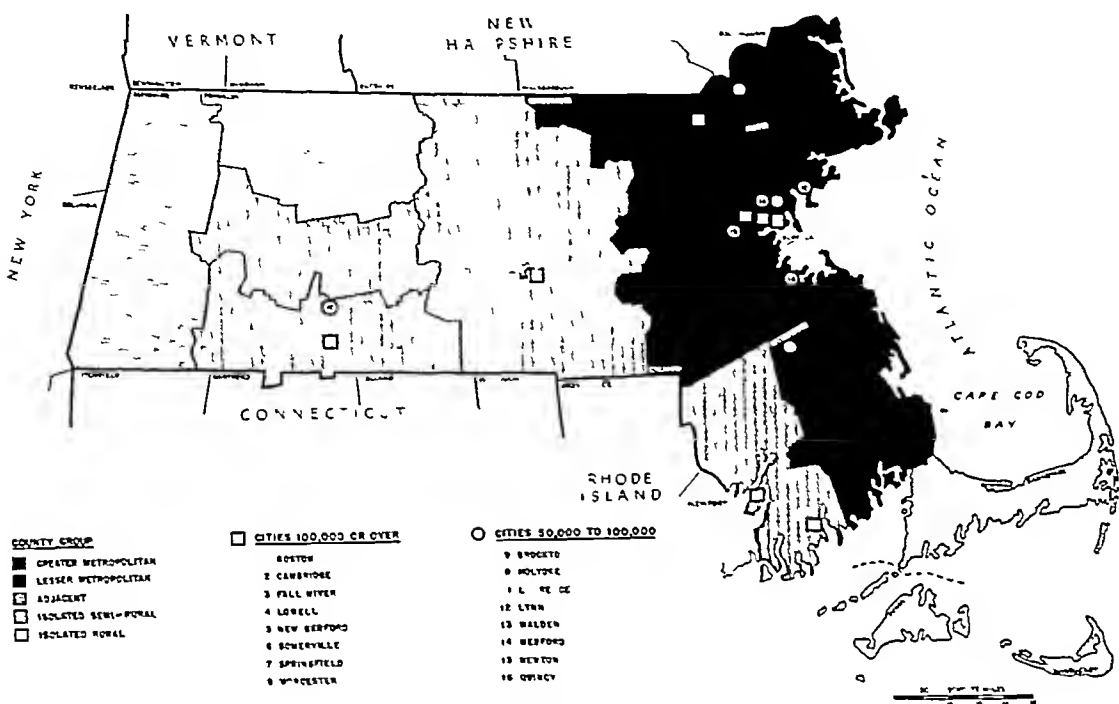


FIGURE 1 County Groups in Massachusetts

point higher than the national average (34.8 per thousand live births)

Massachusetts has an aging population. A third of the inhabitants of the United States, but only a fourth of those in Massachusetts, are under the age of fifteen years.

The Commonwealth has many fewer children living in rural areas than in the rest of the country. Thirty-seven per cent of those in the United States but only 11 per cent of the children in Massachusetts live in "isolated counties."

Responsibility for the maintenance of most official public-health services for children rests with the 351 cities and towns in the Commonwealth. Many of these are small municipalities financially incapable of supporting adequate, modern, full-time health services. Although this multiplicity of governmental units preserves independence and local autonomy, it results in inadequate financing, supervision and integration of health activities.

The findings of the Massachusetts study cannot all be compressed into the confines of this sum-

marized report. The rate of medical care is exceeded only by that in Nevada and New York.

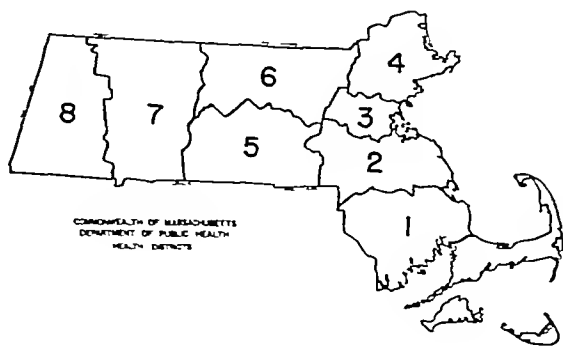


FIGURE 2 Health Districts in Massachusetts

Three fourths of the total consists in visits to children by medical practitioners (Fig 3). Out of a total of 20.3 children per day per 1000 children under

MEDICAL PROGRESS

CHILD HEALTH SERVICES IN MASSACHUSETTS

JAMES MARVIN BATY, M.D.,* AND LENDON SNEDEKER, M.D., M.P.H.†

BOSTON

THE American Academy of Pediatrics has completed a nation-wide study of health services for children. The findings were published by the Commonwealth Fund in April of this year, and have already led to action to improve the health of the nation's children. The study originated in 1944 when the Committee on Post-War Planning reported to the membership of the Academy on the general situation regarding the health of the country's children and recommended that a survey of existing health services be made before any future health program was undertaken. At the same time legislation was pending in Congress that threatened radically to change the nature of medical practice. The study was to ascertain the extent and distribution of present services to children whether provided by professional men in practice, by hospitals and clinics, or by voluntary and official community health agencies.

The Academy study began in North Carolina in the fall of 1945. Other state studies were started in the spring of 1946, following procedures set by the Committee for the Study of Child Health Services, with a central office under the leadership of Dr. John P. Hubbard, the executive director. The results of these studies are now being published in most of the states and recommendations are being made regarding future action, state by state, in the light of local conditions.

This effort is striking evidence of the collective concern of the physicians and dentists of the country for the welfare of children. It is the first time that doctors have pooled their voluntary efforts and inquired into the facilities serving the nation's child population. The survey was made by those directly responsible for rendering health service, and the recommendations are based on facts viewed in the light of a knowledge of local conditions within the states.

In the development of the survey it was left to the initiative of each state chairman to develop an organization in his state, make plans for the distribution and collection of schedules, finance the work and arrange for the reporting of the findings. The central office was responsible for setting the procedures to be followed, for tabulating the data and for returning information to the states for their own use.

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†Executive secretary, Massachusetts Study of Child Health Services.

The Massachusetts study corroborates and emphasizes some of the national findings of the Academy. The importance of the general practitioner in caring for children and the uneven distribution of medical services are both apparent. In Massachusetts, as in the country generally, three fourths of the private medical care of children is supplied by general practitioners. They take care of most of the sick children and also, as a group, do most of the well-child supervision.

Massachusetts, in common with most of the New England states, possesses certain characteristics that set it off from the rest of the country. The population is older. Per-capita incomes are high. There are many small and independent agencies serving children, and official health activities are administered by the local city or town rather than by the county.

MASSACHUSETTS STUDY

The Massachusetts Study of Child Health Services was organized in the spring of 1946 and its report, of which this article is a digest, has recently been published by the American Academy of Arts and Sciences.†

In tabulating data and for comparing sectional differences in health service the Academy study has compiled its information by county and by "metropolitan character of county." This statistical device, which classifies counties according to both population density and proximity to centers of population, is of less use in Massachusetts, where there are only fourteen counties and the population is more uniformly distributed than elsewhere. There are only three "isolated" counties in the Commonwealth: Barnstable, Dukes and Nantucket. Comparatively rural areas in several other counties are obscured (Fig. 1). For this reason Massachusetts data have also been tabulated by health districts, since these seem more adequately to bring out variations in service. Furthermore, they correspond to the present administrative areas of the Massachusetts Department of Public Health (Fig. 2).

Detailed information regarding the collection of data for the Massachusetts study will be found in the complete report to which reference has already been made.

†American Academy of Arts and Sciences, *Health Services for Massachusetts Children*. Special publication, 1949.

amounted to 4.06 child visits per physician, or 20.1 child visits per 1000 children per day. General practitioners made three quarters of these visits.

Care to children constitutes almost a third of the practice of the general practitioner. Of 18,984 visits to patients of all ages, 30.8 per cent were made to children under the age of fifteen.

About a third of all general practitioners do major surgical operations on their child patients, half do

Place of Health Supervision in Medical Service to Children

Health supervision constitutes nearly a third of the medical service given to children. In addition to furnishing health service in private practice, doctors participate in various types of community health service.

For the whole United States 26 per cent of the child care provided by the general practitioner is for

TABLE 2 Total Medical and Dental Service for Children in Massachusetts, United States and Selected States *

SOURCE OF DATA	CHILDREN UNDER MEDICAL CARE per day per 1000 children	CHILD VISITS BY PHYSICIANS per day per 1000 children	CHILDREN UNDER DENTAL CARE per day per 1000 children	PRE SCHOOL CHILDREN UNDER HEALTH SUPERVISION per day per 1000 children
United States	13.8	13.5	3.3	5.5
Massachusetts	20.3	20.1	7.2	9.9
Highest state	22.9	21.8	7.2	10.7
Lowest state	7.7	7.8	0.9	1.9
National ranking of Massachusetts	3.0	3.0	1.0	2.0

*Based on data contained in American Academy of Arts and Sciences, *Health Services for Massachusetts Children*. Special publication 1949.

tonsillectomies, and four fifths are consulted for advice regarding problems in infant feeding.

Ratio of Pediatricians to General Practitioners

Massachusetts ranks fifth among the states in the number of children per pediatrician. There is 1 pediatrician for every 5360 children, as compared with one for 10,299 in the United States.

Pediatricians are younger than the run of practitioners. The median age for pediatricians in Massa-

health supervision. Over twice this amount is furnished by pediatricians (54 per cent). In Massachusetts general practitioners devote 33 per cent and pediatricians 62 per cent of their time with children to health service (Fig. 5).

The doctor is also actively engaged in various types of community health services. Of 1259 phy-

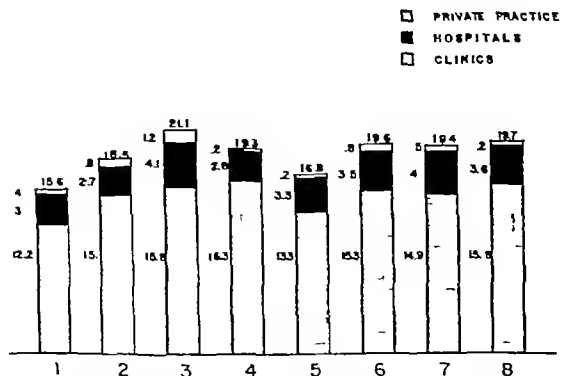


FIGURE 4 Rates for Total Medical Service by Health District in Massachusetts, Expressed as Children under Care per Day per 1000 Children

chusetts is forty-five years. Sixty-six per cent of general practitioners and 76 per cent of pediatricians are under the age of fifty-five years.

Ninety-seven per cent of the 180 pediatricians registered by the Massachusetts Study were located in cities of over 10,000 population.

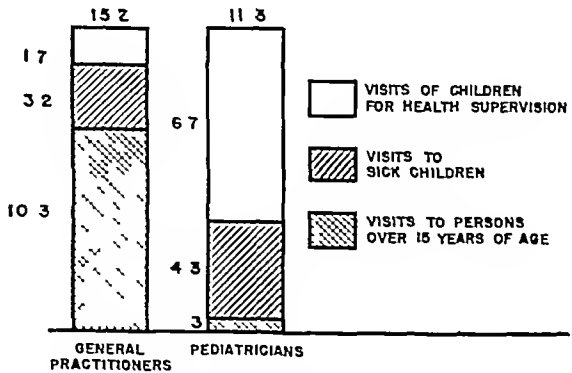


FIGURE 5 Proportion of Practice Devoted to the Care of Well and Sick Children by General Practitioners and Pediatricians in Massachusetts (Average Number of Visits per Day)

cians reporting, 13 per cent had worked in well-child conferences during the month preceding the survey, and about an equal number had worked with school health services.

Hospital Privileges for Care of Children

Hospital privileges for the care of children are restricted for a fifth of practitioners. Nineteen per cent of 1597 physicians reporting said that they were not permitted to care for their child patients in the nearest hospital admitting children.

medical care, 151 were visited by physicians in their homes or visited a doctor's office

There are over twice as many children in Massachusetts under dental care as there are in the whole

Proportion of Medical Service for Health Supervision

About 30 per cent of the children under care on an average day are receiving health supervision Two

TABLE 1 Population, Income and Mortality of United States, Massachusetts and Selected States *

SOURCE OF DATA	CHILD POPULATION IN ISOLATED COUNTIES	CHILDREN IN TOTAL POPULATION	PER CAPITA INCOME 1944-46	INFANT MORTALITY IN 1946
	%	%	\$	per thousand live births
United States average	37	25.0	1,141	33.8
Massachusetts	1	21.8	1,289	31.6
Highest state	100	34.5	1,579	28.2
Lowest state†	8	19.8	559	27.2

*Based on data contained in American Academy of Arts and Sciences Health Services for Massachusetts Children Special publication, 1949

†Other than Massachusetts for percentage of children in isolated counties

United States There are 7.2 children per 1000 children under care on an average day, compared with 3.3 per 1000 for the whole country Nine

thirds of this is furnished by the general practitioner Well-child conferences account for about one tenth of all health supervision

Distribution of Medical and Dental Care

Children in the three "isolated" counties (Barnstable, Dukes and Nantucket) receive two thirds as much pediatric care, one third as much specialist care, one fifth as much clinic care and about half as much hospital service as their fellows in the other counties of the Commonwealth Similarly, the rate for dental care is lower in these isolated counties (5.6 per 1000, contrasted with 7.4 per 1000 for metropolitan and adjacent counties)

If medical care is considered by health district it is clear that children in Districts 1 and 5 receive the lowest rates of service (Fig 4)

Distribution of Physicians and Dentists

Massachusetts ranks second among the states with reference to the number of physicians in private practice There is 1 physician for every 855 people, and 1 for every 202 children under the age of fifteen Of all practitioners, 61 per cent are family doctors, 4 per cent are pediatricians, and 35 per cent are specialists in other fields Ninety per cent of medical practitioners live in cities with populations of 10,000 or more, which contain 83.5 per cent of the inhabitants of the Commonwealth There are fewer doctors in Districts 1, 2 and 6 in proportion to the child population

Massachusetts ranks fifth with respect to the number of dental practitioners There is 1 dentist for every 368 children Over 90 per cent of dentists live in cities of 10,000 or more The proportion of dentists to population in District 3 is twice that in Districts 1 and 6

Contribution of General Practitioner to the Care of Children

On an average day the physicians in Massachusetts made a total of 19,418 visits to children This

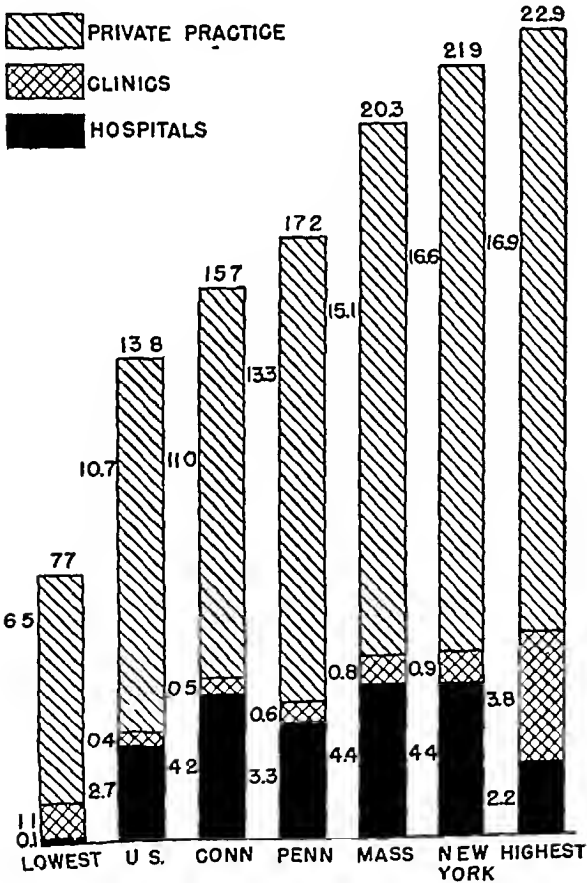


FIGURE 3 Total Volume of Medical Care for Children on One Day per 1000 Children in Massachusetts Comparison with the United States and Selected States

tenths of the dental care to children is furnished by dental practitioners, and one tenth by dental clinics The comparative figures on medical and dental service are shown in Table 2

than half of these have separate pediatric clinics. There is only one hospital outpatient department in the "isolated" counties (Barnstable, Dukes and Nantucket). Clinic facilities are less in Districts 2, 5, 7 and 8. Special pediatric clinics are almost all located in the more urban areas.

Care in Dental Clinics

The rate of dental-clinic care of children is high in Massachusetts, but there is considerable difference in the rates of care in the various health districts.

Children in the neighborhood of Metropolitan Boston (District 3) receive much more care than those in other districts, whether this is expressed in terms of dentist hours, patients, visits or examinations. Official dental agencies care for more children, but provide less service to the individual child.

Distribution of Public-Health Nursing Service

Although Massachusetts ranks fourth among the states in the amount of public-health nursing service to children, there are inequalities in the distribution of service and a need to increase the proportion of nurses who have had specialized training.

Fifty-nine per cent of the cities and towns in the Commonwealth reported that they maintained some form of public-health nursing service. The distribution of nurses in the state is uneven, and the rates for service vary. There are often several nursing agencies in a single city or town without provision for co-ordination of effort. Only a small percentage of nurses have had special training in public health. Of 854 nurses 686, or 80 per cent, had had no formal training in a recognized program of public-health nursing, or had completed less than one academic year.

Character of Medical Service for School Children

Some kind of medical service is almost universally available to the school children of Massachusetts, but there is great variation in the character of that service. Although there are no counties without school health supervision, seven towns fail to report any service. Eighty-eight per cent of the physicians in the public schools are general practitioners. Only 47 of 602 school physicians are pediatricians. Less than half the 552 school nurses reported are employed full time.

Health Supervision for Children of Pre-school Age

Massachusetts ranks second among the states in the amount of health supervision for children of pre-school age. About one tenth of such care is provided by well-child conferences.

The rates of care for well-child conferences (Fig. 6) are not uniform and are lowest in Health Districts 4 and 5. Over half the 276 well-child conferences reported are maintained in whole or in part by official agencies. Children make an average of two and eight-tenths visits per year each. In a few towns conferences are held only twice a year.

General practitioners and pediatricians together provide about four fifths of the medical service at these clinics. Most of them are part-time, paid workers. Five per cent of the general practitioners and 13 per cent of the pediatricians serve without compensation.

Service in Well-Child Conferences

There is considerable variation in the kind of service available in well-child conferences. Infants receive more care than older children. Practically all clinics provide nursing service, and medical advice regarding feeding and child management is

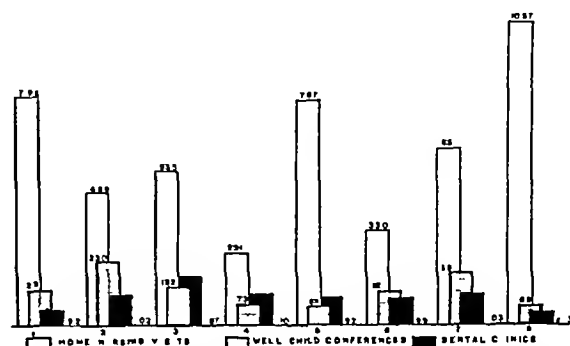


FIGURE 6 Yearly Rates per 1000 Children for Three Types of Community Health Service in Massachusetts by Health District. Well-child conference visits are expressed per 1000 children under five years of age.

available at 83 per cent of all sessions. Approximately two thirds of the sessions provide nutrition service, and one fifth psychologic or psychiatric advice when needed.

Immunization in Well-Child Conferences

Well-child conferences are not effective in immunizing children against communicable disease. Only a small percentage of sessions routinely provide immunization. One third immunize against diphtheria, whooping cough and smallpox. In clinics where the number of children immunized is known, slightly less than half the children are vaccinated and about one quarter immunized against diphtheria and whooping cough. The practices followed in various clinics are not uniform and often fail to recognize the need for immunization in the first two years of life, rather than in the pre-school period.

Care of Physically Handicapped Children

Facilities for the care of the physically handicapped are fairly evenly distributed throughout the Commonwealth. A large amount of specialized orthopedic and other care to physically handicapped children is provided in hospitals, especially in the teaching centers of Boston, and is not enumerated by the study. Clinics maintained under the Crippled Children's Program limit their services to children

Inadequacies in Hospital and Pediatric Training

The considerable proportion of practice concerned with the medical problems of children and degree of responsibility assumed by the practitioner for the surgical problems of childhood calls for adequate pediatric training. Although the preparation of physicians for practice is continually improving, it is noteworthy that of 1607 general practitioners in Massachusetts 72 per cent reported that they had had no hospital training whatever. A total of 25 per cent had had less than a year of training. Over a third had had less than a month's hospital work in pediatrics before entering practice, and slightly less than a third had had no postgraduate training in pediatrics. Doctors who had had more than a year of hospital training were making 85 per cent of the visits to children.

Deficiencies in the Training of Dental Practitioners

Only half the 1735 dentists reporting had had any training in children's dentistry. Training in the care of children was more frequently reported by older practitioners.

Hospital Facilities for Children in the State as a Whole

The Commonwealth is fifth in number of hospital beds, third in number of children's beds and ninth in the number of child admissions per 1000 children. One twentieth of the 43,084 general-hospital beds for children in the United States are in Massachusetts. Total hospital beds in Massachusetts number 18.2 per 1000 children, and children's beds 2.2 per 1000.

There are 151 general hospitals in the Commonwealth, 140 of which admit children. There are 72 hospitals with pediatric units of 5 or more beds, and 3 pediatric hospitals. More than half the pediatric beds are located within a 25-mile radius of Boston.

Nonprofit hospitals provide nearly three quarters of the available beds for children. Municipal hospitals, with 23.4 per cent of the pediatric beds, care for only 14.2 per cent of the child admissions.

Hospital Facilities for Children in Rural Areas

There are 11.6 general-hospital beds per 1000 children in the "isolated" counties (Barnstable, Dukes and Nantucket), and 18.3 per 1000 in the rest of the State. There are only a quarter of the pediatric beds in isolated counties in proportion to the child population that there are in the State as a whole. There are fewer hospital facilities for children in Districts 1, 2 and 4.

Size of Hospital

Most children are admitted to large general hospitals with over 100 beds, especially to those with pediatric units, 73.9 per cent of all child admissions occur in hospitals with more than 100 beds, and 86 per cent in hospitals with pediatric units.

Use of Pediatric Beds

Pediatric beds are not fully utilized. The occupancy rate for pediatric beds in the Commonwealth averages 60 per cent, but rates as low as 45 per cent have been noted for certain hospitals.

Effect of Size and Character of Hospitals on Quality of Care

Hospital facilities for children improve with size, and hospitals with pediatric units are more adequately staffed and equipped. Small proprietary hospitals are limited in laboratory facilities and trained personnel for the management of pediatric cases.

Isolation Facilities for Infants and Graduate-Nursing Supervision

Thirty-one per cent of child admissions occur in hospitals with no graduate nurse in charge of the pediatric unit. In 36 per cent infants, other than newborn, are not segregated from older children, and the risk of intercurrent infections is correspondingly greater.

Births in Hospitals

In 1946, 97.2 per cent of the births in Massachusetts occurred in hospitals. The percentage was slightly lower in the isolated counties (89.7) and nonwhite mothers had slightly more births outside hospitals in the same area. The average length of hospital stay for newborn infants was nine and four-tenths days.

Neonatal Infection

Certain conditions in newborn nurseries predispose to neonatal infection.

Twenty-three per cent of the births in Massachusetts hospitals during the report year occurred in hospitals without a separate formula room, and 45 per cent in hospitals lacking isolation facilities for sick infants or for those suspected of being ill.

Care of Mentally Sick, Mentally Deficient and Epileptic Children

Two thirds of the facilities for the convalescent and chronic care of children are reserved for the care of mentally sick, the mentally deficient and epileptic patients. Waiting lists in institutions caring for such children are very long, and the amount of supervision by graduate nurses is far less than that in other institutions caring for the chronically sick.

Care in Medical Clinics

The rate of clinic care of children is high in Massachusetts, being twice that for the United States average. However, clinics account for only 5 per cent of all medical service to children.

Eighty per cent of all the clinics caring for children are in general hospitals of over 100 beds, and more

in his own office. Modern transportation reduces the necessity for providing a variety of outpatient services, but the poor, who are in greatest need of corrective services, are least able to travel. Programs for the correction of physical defects will continue to be relatively ineffective and unnecessarily expensive as long as diagnostic and corrective services are inconveniently distant from the affected child.

A few general points might be made regarding community health services for children. Well-child conferences cannot be considered really effective until they provide the medically indigent with continuously accessible facilities for examination, immunization and medical advice. An average of two and eight-tenths visits per year is not enough to constitute regular health supervision. The average well-child conference is not effective in immunizing children against the important communicable diseases. Although these conferences should not be the only agencies providing immunization, they should be more effective with the clientele they serve. At present the diversity of health agencies, their physical separation and the resultant partition of medical service discourage the medically indigent from seeking attention. It would be advantageous to centralize health services more often and to locate them, where possible, in or near the local hospital.

If towns wish to maintain their own services, there should be some provision for unification and supervision of their work. One or more adequately paid pediatric consultants could do much to improve the present situation. The solution of many child health problems would be facilitated if agencies were working more often in conjunction with local health units of adequate size, and employing well trained, full-time personnel.

RECOMMENDATIONS

In consideration of the large proportion of medical practice that is concerned with children, medical schools should devote more attention to maternal and child health in their curriculums, placing emphasis on preventive technics applicable in private practice.

In addition to their present educational activities, the Massachusetts Medical Society, the Massachusetts Chapter of the American Academy of Pediatrics and the New England Pediatric Society should sponsor programs for training in maternal and child health for all professional persons caring for children, with particular emphasis upon those preparing for general practice.

Dental schools should likewise stress preventive dentistry and its application to childhood in their curriculums. Research should include an energetic inquiry into methods of dental prophylaxis. Where dental personnel is inadequate greater use of auxiliary personnel should be considered.

Means should be found for encouraging young physicians to settle in the parts of the Commonwealth where children are now receiving less than the average amount of medical service.

Wherever possible hospital privileges should be extended to physicians who show an active interest in increasing their professional ability by availing themselves of opportunities for postgraduate education.

The present co-operative efforts of the Massachusetts Medical Society and the Massachusetts Department of Public Health to reduce maternal mortality should be intensified. Some investigation of infant deaths should be undertaken. The present system for reporting infant births and deaths, especially those among premature infants, needs improving.

Local hospitals should increase their existing safeguards against cross infection in children's wards and nurseries for newborn infants. Adequate isolation facilities are of major importance.

Construction of new hospital facilities for children should be undertaken only after due study of local needs and the present utilization of existing beds. The limitations of the community hospital in treating the diseases of children and its function as a health center deserve reconsideration.

The Massachusetts Department of Public Health should be enabled to provide pediatric, nursing and other consultants to work on the problem of correlating and improving local health work for children.

Present facilities for the hospital care of children with mental deficiency and convulsive disorders should be increased.

Well-child conferences should increase the frequency of their health supervision and intensify their efforts to detect and follow children with defects. The efficiency of the present immunization program should be improved and present policies should be scrutinized. Opportunities should be increased for the training of doctors conducting well-child conferences.

Dental clinics in the Commonwealth should be increased in areas where present services are below average.

Public-health nursing services should be more adequately supervised and integrated. Under present conditions service is unevenly distributed, and there is too much opportunity for duplication of effort. Standards for the employment and training of public-health nursing personnel need improving.

The medical and dental professions should give support to the recommendations made in the *Report of the Special Commission to Study and Investigate Certain Public Health Matters* (House Document 2100, 1949). Those having special importance are the development of local full-time health services, improvement in present methods for collecting and transmitting vital statistics, and the provision of adequate standards of employment and remuneration for public-health personnel.

with orthopedic and plastic conditions, and to those with speech defects

Care of Mentally Handicapped Children

The existing services for mentally handicapped children are too limited. There are 21 mental-hygiene clinics operated by the Massachusetts Department of Mental Health or the city of Boston. There are only 3 independent clinics under voluntary auspices, and 7 voluntary hospitals with special mental-hygiene facilities. All the clinics have complete staff service, which means at least a part-time psychiatrist, a psychologist and a social worker. Nearly two thirds of the clinics have a full-time psychiatrist in attendance.

DISCUSSION

The foregoing summary gives abundant evidence of the high standard of medical care now provided for Massachusetts children. However, a large number of doctors and dentists, a high rate for health supervision and a large percentage of births in hospitals have not produced an exceptionally low mortality or a great reduction in dental decay, and have not been effective in immunizing a large percentage of the children attending well-child conferences. The twelfth wealthiest state in the Union should not stand in twentieth place in infant mortality or twenty-second in maternal death rate. Although it is agreed that such rates are not the only measure of the efficacy of a health program, one does not expect a highly urban state such as Massachusetts to be outstripped by rural states like Nebraska and North Dakota, or by such nearly comparable neighbors as Rhode Island and Connecticut. These mortality rates seem unnecessarily high.

Medical care for children in Massachusetts, as well as in the rest of the United States, is unevenly distributed and least available in rural areas. In view of the small proportion of children living in the isolated counties of Massachusetts, this may not be as significant as in other states, where the problems of distance make it difficult to obtain medical service. However, such inequalities need investigating, and will have to be eliminated before it can be said that all children in the Commonwealth have an equal chance to survive infancy and grow to competent majority.

The general practitioner, who is by far the most important person providing medical service to children, needs more pediatric training, both in medical school and in hospital. In the realm of postgraduate pediatric education, a review of programs sponsored by the Massachusetts Medical Society or by the New England Postgraduate Assembly discloses relatively few papers dealing with the problems of children. This is by no means meant as a reflection on the very considerable program now being carried out by the Society, in co-operation with the Massachusetts Department of Public Health, both at weekly sessions held for two months

each year in Boston and at the meetings of its district medical societies.

There is another opportunity for improving the pediatric education of physicians. It was noted that nearly a fifth of physicians lacked hospital privileges in near-by institutions to which their child patients were admitted. With further means developed for including these physicians in the educational activities of these hospitals and with the elimination of substandard medical schools, eventually more doctors should be able to enjoy hospital privileges.

What has been said of physicians is equally true of dental practitioners. The small number of dentists who specialize in children's work or in orthodontia is evidence of the relative lack of interest in the dental problems of early life. With the dentists now available, or in prospect, it is practically impossible to meet present demands for restorative dental work, even if the means could be found to pay for it. It is probably advisable to extend the use of auxiliary dental personnel, but especially to develop effective mass prophylaxis against dental decay.

Hospital facilities for children are unevenly distributed throughout the Commonwealth. Part of this inequality may be compensated for by the transportation of sick children to suitable pediatric centers, but the situation calls for some critical consideration. It is not only a lack of beds but also the manner in which they are utilized and safeguarded that is important. About a third of the hospitals admitting children have no graduate nursing supervision of their pediatric beds. There is evidence that some hospitals lack adequate provision for safeguarding infants, including newborn, against intercurrent infection in the hospital. There is evidence that pediatric beds are not being fully utilized. Construction of new beds for children should probably not be undertaken until it is clear that present use is optimal. These are matters that should be considered and, when necessary, improved through the local action of practitioners interested in the welfare of children. The Division of Hospitals of the Massachusetts Department of Public Health is an important factor in improving hospital standards. It should be sufficiently provided with personnel so that it is able to temper its present regulatory power with a large amount of educational work. More often hospital standards should be based on the collective experience of practicing physicians, and this is well exemplified by the recent report of the Committee on the Fetus and Newborn of the American Academy of Pediatrics.

The prime need in the field of chronic care is to provide more beds for the mentally deficient and epileptic.

Outpatient facilities are fewer in the isolated areas of the Commonwealth. On the other hand the practitioner in the country runs his own outpatient department along with his practice. A relative lack of clinics may be chiefly important in the diagnostic facilities that the average physician cannot provide.

in his own office. Modern transportation reduces the necessity for providing a variety of outpatient services, but the poor, who are in greatest need of corrective services, are least able to travel. Programs for the correction of physical defects will continue to be relatively ineffective and unnecessarily expensive as long as diagnostic and corrective services are inconveniently distant from the affected child.

A few general points might be made regarding community health services for children. Well-child conferences cannot be considered really effective until they provide the medically indigent with continuously accessible facilities for examination, immunization and medical advice. An average of two and eight-tenths visits per year is not enough to constitute regular health supervision. The average well-child conference is not effective in immunizing children against the important communicable diseases. Although these conferences should not be the only agencies providing immunization, they should be more effective with the clientele they serve. At present the diversity of health agencies, their physical separation and the resultant partition of medical service discourage the medically indigent from seeking attention. It would be advantageous to centralize health services more often and to locate them, where possible, in or near the local hospital.

If towns wish to maintain their own services, there should be some provision for unification and supervision of their work. One or more adequately paid pediatric consultants could do much to improve the present situation. The solution of many child health problems would be facilitated if agencies were working more often in conjunction with local health units of adequate size, and employing well trained, full-time personnel.

RECOMMENDATIONS

In consideration of the large proportion of medical practice that is concerned with children, medical schools should devote more attention to maternal and child health in their curriculums, placing emphasis on preventive techniques applicable in private practice.

In addition to their present educational activities, the Massachusetts Medical Society, the Massachusetts Chapter of the American Academy of Pediatrics and the New England Pediatric Society should sponsor programs for training in maternal and child health for all professional persons caring for children, with particular emphasis upon those preparing for general practice.

Dental schools should likewise stress preventive dentistry and its application to childhood in their curriculums. Research should include an energetic inquiry into methods of dental prophylaxis. Where dental personnel is inadequate greater use of auxiliary personnel should be considered.

Means should be found for encouraging young physicians to settle in the parts of the Commonwealth where children are now receiving less than the average amount of medical service.

Wherever possible hospital privileges should be extended to physicians who show an active interest in increasing their professional ability by availing themselves of opportunities for postgraduate education.

The present co-operative efforts of the Massachusetts Medical Society and the Massachusetts Department of Public Health to reduce maternal mortality should be intensified. Some investigation of infant deaths should be undertaken. The present system for reporting infant births and deaths, especially those among premature infants, needs improving.

Local hospitals should increase their existing safeguards against cross infection in children's wards and nurseries for newborn infants. Adequate isolation facilities are of major importance.

Construction of new hospital facilities for children should be undertaken only after due study of local needs and the present utilization of existing beds. The limitations of the community hospital in treating the diseases of children and its function as a health center deserve reconsideration.

The Massachusetts Department of Public Health should be enabled to provide pediatric, nursing and other consultants to work on the problem of correlating and improving local health work for children.

Present facilities for the hospital care of children with mental deficiency and convulsive disorders should be increased.

Well-child conferences should increase the frequency of their health supervision and intensify their efforts to detect and follow children with defects. The efficiency of the present immunization program should be improved and present policies should be scrutinized. Opportunities should be increased for the training of doctors conducting well-child conferences.

Dental clinics in the Commonwealth should be increased in areas where present services are below average.

Public-health nursing services should be more adequately supervised and integrated. Under present conditions service is unevenly distributed, and there is too much opportunity for duplication of effort. Standards for the employment and training of public-health nursing personnel need improving.

The medical and dental professions should give support to the recommendations made in the *Report of the Special Commission to Study and Investigate Certain Public Health Matters* (House Document 2100, 1949). Those having special importance are the development of local full-time health services, improvement in present methods for collecting and transmitting vital statistics, and the provision of adequate standards of employment and remuneration for public-health personnel.

with orthopedic and plastic conditions, and to those with speech defects

Care of Mentally Handicapped Children

The existing services for mentally handicapped children are too limited. There are 21 mental-hygiene clinics operated by the Massachusetts Department of Mental Health or the city of Boston. There are only 3 independent clinics under voluntary auspices, and 7 voluntary hospitals with special mental-hygiene facilities. All the clinics have complete staff service, which means at least a part-time psychiatrist, a psychologist and a social worker. Nearly two thirds of the clinics have a full-time psychiatrist in attendance.

DISCUSSION

The foregoing summary gives abundant evidence of the high standard of medical care now provided for Massachusetts children. However, a large number of doctors and dentists, a high rate for health supervision and a large percentage of births in hospitals have not produced an exceptionally low mortality or a great reduction in dental decay, and have not been effective in immunizing a large percentage of the children attending well-child conferences. The twelfth wealthiest state in the Union should not stand in twentieth place in infant mortality or twenty-second in maternal death rate. Although it is agreed that such rates are not the only measure of the efficacy of a health program, one does not expect a highly urban state such as Massachusetts to be outstripped by rural states like Nebraska and North Dakota, or by such nearly comparable neighbors as Rhode Island and Connecticut. These mortality rates seem unnecessarily high.

Medical care for children in Massachusetts, as well as in the rest of the United States, is unevenly distributed and least available in rural areas. In view of the small proportion of children living in the isolated counties of Massachusetts, this may not be as significant as in other states, where the problems of distance make it difficult to obtain medical service. However, such inequalities need investigating, and will have to be eliminated before it can be said that all children in the Commonwealth have an equal chance to survive infancy and grow to competent majority.

The general practitioner, who is by far the most important person providing medical service to children, needs more pediatric training, both in medical school and in hospital. In the realm of postgraduate pediatric education, a review of programs sponsored by the Massachusetts Medical Society or by the New England Postgraduate Assembly discloses relatively few papers dealing with the problems of children. This is by no means meant as a reflection on the very considerable program now being carried out by the Society, in co-operation with the Massachusetts Department of Public Health, both at weekly sessions held for two months

each year in Boston and at the meetings of its district medical societies.

There is another opportunity for improving the pediatric education of physicians. It was noted that nearly a fifth of physicians lacked hospital privileges in near-by institutions to which their child patients were admitted. With further means developed for including these physicians in the educational activities of these hospitals and with the elimination of substandard medical schools, eventually more doctors should be able to enjoy hospital privileges.

What has been said of physicians is equally true of dental practitioners. The small number of dentists who specialize in children's work or in orthodontia is evidence of the relative lack of interest in the dental problems of early life. With the dentists now available, or in prospect, it is practically impossible to meet present demands for restorative dental work, even if the means could be found to pay for it. It is probably advisable to extend the use of auxiliary dental personnel, but especially to develop effective mass prophylaxis against dental decay.

Hospital facilities for children are unevenly distributed throughout the Commonwealth. Part of this inequality may be compensated for by the transportation of sick children to suitable pediatric centers, but the situation calls for some critical consideration. It is not only a lack of beds but also the manner in which they are utilized and safeguarded that is important. About a third of the hospitals admitting children have no graduate nursing supervision of their pediatric beds. There is evidence that some hospitals lack adequate provision for safeguarding infants, including newborn, against intercurrent infection in the hospital. There is evidence that pediatric beds are not being fully utilized. Construction of new beds for children should probably not be undertaken until it is clear that present use is optimal. These are matters that should be considered and, when necessary, improved through the local action of practitioners interested in the welfare of children. The Division of Hospitals of the Massachusetts Department of Public Health is an important factor in improving hospital standards. It should be sufficiently provided with personnel so that it is able to temper its present regulatory power with a large amount of educational work. More often hospital standards should be based on the collective experience of practicing physicians, and this is well exemplified by the recent report of the Committee on the Fetus and Newborn of the American Academy of Pediatrics.

The prime need in the field of chronic care is to provide more beds for the mentally deficient and epileptic.

Outpatient facilities are fewer in the isolated areas of the Commonwealth. On the other hand the practitioner in the country runs his own outpatient department along with his practice. A relative lack of clinics may be chiefly important in the diagnostic facilities that the average physician cannot provide.

time of examination two weeks later, however. Five weeks before entry he was admitted to another hospital and treated with aerosol penicillin. During a four-week period of hospitalization the symptoms increased in severity. At home, during the week prior to readmission to this hospital, ankle swelling appeared, and dyspnea became very marked.

Physical examination showed a well nourished man, who was coughing and dyspneic. There was no venous distention in the neck. The anteroposterior diameter of the chest was increased. The chest was hyperresonant, except at the right base. Diffuse rhonchi were heard throughout. Breath sounds were decreased at the right base. Auricular fibrillation was present, with an apical rate of 100 and a pulse rate of 80. The first heart sound at the apex had a snapping quality. The pulmonic second sound was louder than the aortic. No murmurs were heard. The blood pressure was 125 systolic, 90 diastolic.

The white-cell count was 12,000, with a normal differential. The hemoglobin was 15 gm. The urine had a specific gravity of 1.020 and gave ++ to +++ tests for albumin, and there were rare red and white blood cells in the sediment. The sedimentation rate was 19 mm. per minute. The stools were brown, and the guaiac test was ++. Sputum cultures were repeatedly negative for beta-hemolytic streptococci and pneumococci. Repeated blood cultures were negative.

An electrocardiogram showed a coarse auricular fibrillation and right-axis deviation. Chest x-ray study revealed an enlarged heart shadow and moderate congestion in both lungs. There was some fluid present at the right base. No atelectasis was seen.

During the hospital stay the patient ran a low-grade fever, ranging between 99 and 102°F. Dyspnea and cough, accompanied by blood-streaked sputum, persisted. Therapy included digitalis, aerosol penicillin and mercurhydrin. After three weeks in the hospital there was no improvement. Marked weakness developed. Chemical examination of the blood at this time showed a nonprotein nitrogen of 34 mg. per 100 cc., and a sodium of 110.6, chloride of 70 and carbon dioxide of 29.2 milliequiv. per liter. Vigorous therapy with salt by mouth (2 gm. and more daily) resulted in no improvement. The highest serum sodium obtained was 114.1 and the highest chloride 75 milliequiv. per liter.

He complained of severe abdominal discomfort and persistent anorexia. Extreme weakness continued. The liver was enlarged and tender. Five weeks after readmission he became unresponsive. The pulse became unobtainable and over a period of two hours the respirations gradually slowed and ceased.

DIFFERENTIAL DIAGNOSIS

DR. CONGER WILLIAMS: Nothing is said about cyanosis so I assume that it was not present. In view of the complexity and length of this account, I might pause and consider briefly a few possibilities.

This is a middle-aged man who came in with

a history of cough for ten years, dyspnea for eight years and an important cardiac arrhythmia—namely, auricular fibrillation. In a man of this age a very common cause of auricular fibrillation is mitral stenosis, especially with a history of this length. Could mitral stenosis alone account for such a long history of cough and dyspnea? It could, but there are two points that must be mentioned, which perhaps are a little against mitral stenosis as the only cause for his symptoms: the amount of productive sputum that the patient had over a period of several years and the severity of the cough. These two reservations suggest another possibility,—chronic pulmonary disease, either as the only lesion or complicating mitral stenosis. It is quite conceivable that he had the syndrome of chronic bronchitis, emphysema and asthma over many years. I cannot tell from the physical examination reported whether the chest showed the structural changes expected in such a situation.

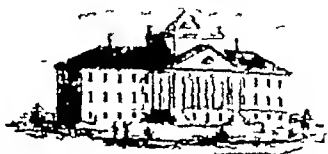
DR. HELEN PITTMAN: We thought it did.

DR. WILLIAMS: So perhaps that possibility is a little stronger. It was mentioned earlier in the history that this patient worked in a steel mill twenty years before admission, where he was exposed to large amounts of metal dust. This brings up the possibility of pneumoconiosis, but I can do nothing more than suggest the possibility since there was no known exposure to silica or asbestos. Did this man have enough pulmonary disease to give him chronic heart disease, namely, chronic cor pulmonale, which, complicated by auricular fibrillation, might account for congestive failure? Auricular fibrillation as a complication of cor pulmonale, especially at this age, is unusual but not impossible. Another thing that seems quite evident is that regardless of the cause of the chronic symptoms, he had an acute infection, possibly in the lungs, since he had chills just before entry, and fever and leukocytosis in the hospital. It is possible that he had pneumonia, complicating old chronic pulmonary infection.

If the red-cell count of 6,700,000 represents a real polycythemia, that finding is in favor of chronic pulmonary disease. We do not very often see polycythemia in heart disease unless there is a right-to-left shunt. However, this may not have been real polycythemia, but merely a result of hemoconcentration from fever, profuse sweating and so forth. I do not believe that congestive failure, although quite marked, could account entirely for the +++ test for albumin in the urine, but it is possible. Rusty sputum goes with either a chronic or an acute history of pulmonary involvement. It is possible that the nephrotic syndrome was suspected at this time, judging from some of the tests done. Either of the bromsulfalein figures could be consistent with various degrees of congestive heart failure.

After examination of the electrocardiogram and observation of the chest leads, it is more evident that he had right ventricular enlargement. The

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 35381

PRESENTATION OF CASE

First admission A forty-one-year-old Italian shoemaker was admitted to the hospital complaining of a cold in the chest.

For ten years before admission the patient had a severe cough, which increased in frequency and severity up to admission. Eight years before entry dyspnea appeared, especially after bouts of coughing. A chest x-ray examination was said to have demonstrated some "bronchial difficulty, but no serious disease." Five years before admission the dyspnea had become so severe that he was forced to take an easier job at which he could sit down. Two years before entry, on the advice of his physician, digitalis was started and maintained up to admission. There had been no weight loss. There was an inconclusive history of one or two slight episodes of ankle edema. He had had night sweats for many years. Orthopnea requiring three pillows at night was present for three years. A cupful of dark-brown, nonfoul-smelling sputum was raised every day. Four days before admission he "caught a cold in his chest" and had two severe chills during which his teeth chattered. The cough increased in severity, and he felt feverish.

He had worked in a steel mill twenty years before admission and was exposed to large amounts of metal dust and fumes but not to silica.

Physical examination showed a well developed man, breathing quickly with an audible wheeze. The heart was slightly enlarged to the left and moderately enlarged to the right. The rhythm was that of a rapid auricular fibrillation, with an apical rate of 130 and a radial pulse rate of 80. Numerous sibilant and musical rales and increased tactile fremitus were present over the right posterior chest. The liver edge extended four or five fingerbreadths below the costal margin and was smooth and tender. The fingers were not noticeably clubbed, but the nails were extremely curved. The temperature was 102°F.

Examination of the blood revealed a white-cell count of 15,000, with 78 per cent neutrophils. The hemoglobin was 17 gm., and the red-cell count

and gave a +++ test for albumin, and there were occasional red and white blood cells in the sediment. The sputum was rusty and negative for acid-fast organisms. The stools were guaiac negative. The prothrombin time was 23 seconds (control, 18 seconds). The van den Bergh test was 12 mg per 100 cc direct and 20 mg indirect. The total protein was 7.42 gm per 100 cc, with an albumin of 3.49 gm and a globulin of 3.93 gm (albumin-globulin ratio of 0.89). The cephalin-flocculation test was + in forty-eight hours. The cholesterol was 263 mg, the nonprotein nitrogen 34 mg, and the serum phosphorus 2.8 mg per 100 cc. The alkaline phosphatase was 3 units. A bromsulfalein test showed 22 per cent retention and 8 per cent retention on separate occasions. An electrocardiogram demonstrated auricular fibrillation, with a ventricular rate of 160. Right-axis deviation was present. The T wave in Lead 1 was flat. The ST segments in Lead 2 and 3 were sagging, and the T waves in Lead CF₁, CF₂, and CF₃ were inverted. The S waves in the precordial leads were of greater voltage than normal. The vital capacity was 1.7 liters. X-ray study of the chest demonstrated an enlarged heart without any characteristic configuration, the ratio being 15.7 to 32.2. There was considerable engorgement of the hilar and pulmonary blood vessels. There was a diffuse, hazy increase of density in the left lower chest, with a small amount of fluid in the left pleural cavity.

Digitalis, small doses of quinidine and intramuscular administration of penicillin had no remarkable therapeutic effect. When aerosol penicillin was given the temperature gradually subsided, and the severity of the cough and sputum production diminished. He was discharged one month after admission.

Final admission (three years later) He was followed regularly in the Out-Patient Department. During the entire interval between admissions therapy included digitalis, ammonium chloride and a low-salt diet. Auricular fibrillation was present at each examination. For the first two years he was able to do light work, although exertional dyspnea and orthopnea were marked. In the year before readmission weakness, cough and exertional dyspnea were so great that he was unable to work, spending much of his time in bed. There was no ankle edema. Two and a half years before re-entry on one examination, with the apex rate at 84 and with the patient in the left lateral recumbent position, the first heart sound was sharp, and a distant, rumbling, mid-diastolic murmur was noted. Chest x-ray examination showed no appreciable change in heart size and configuration, although it was evident that the left auricle was enlarged. The lung fields were clear. At intervals carious teeth were extracted while the patient received penicillin intramuscularly. About three months before readmission he complained of several episodes of bloody sputum and a tender swelling in the left leg. There was no tenderness or swelling at

CLINICAL DIAGNOSES

Cardiac insufficiency
Rheumatic heart disease, active
Pulmonary emphysema

DR WILLIAMS'S DIAGNOSES

Rheumatic heart disease mitral stenosis, auricular fibrillation, congestive failure
Chronic bronchitis
Pulmonary embolism?

ANATOMICAL DIAGNOSES

Rheumatic heart disease, with mitral stenosis
Multiple pulmonary embolism and infarction, massive, old and recent
Cardiac hypertrophy, right ventricle (cor pulmonale)
Massive mural thrombus, left auricle, obliterating mitral valve and extending into pulmonary vein
Hydrothorax, right
Central necrosis of liver

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN The autopsy was limited to the chest, unfortunately I cannot answer some of the abdominal questions. We were able to examine a piece of liver and found marked central necrosis. The right pleural cavity contained 3 liters of rather clear fluid.

The startling gross finding was the presence of infarcts of various ages in every lobe of the lung. Most were located in the right lower lobe, one of which was apparently fairly old and had a central necrotic abscess in it, which is very unusual in a bland pulmonary infarct. This infarct was the largest, measuring 8 cm in diameter, with a central cavity of 3 or 4 cm. Although we were unable to find on the gross examination any infarcts that seemed completely healed, we did find in some of the arteries within the lung evidence of old embolism with recanalization, some involving the tiny arteries. Some of the larger vessels had adherent thrombi that were perhaps a year or so old. So it is quite possible that a great deal of the right-sided hypertrophy was due to old embolism of the lung. There was some emphysema but not very much fibrosis of the lung.

The heart was enlarged, weighing about 500 mg, most of the enlargement being due to right-sided hypertrophy. The right ventricle measured 10 mm in thickness, three or four times the normal size, and the right auricle was tremendously distended, much more than the left, which was also dilated. This was surprising, at first glance, because there was severe mitral stenosis. Filling the large left auricle and obliterating the already stenotic mitral valve was a huge mural thrombus, 8 by 5 by 4 cm. The large mural thrombus not only filled the left auricle but extended into the pulmonary vein from the right lower lobe, and since there were many emboli in the pulmonary artery to this lobe, there was probably very little blood getting in and out, thus accounting for the cavitation in the large infarct.

DR WILLIAMS Was that recent?

DR CASTLEMAN It must have been there for some time, because it was adherent and well organized, perhaps for months. We have therefore a number of possibilities to account for the large right ventricle: some emphysema, a severe mitral stenosis, and embolism, both chronic and recent, occurring in the pulmonary circuit.

DR ALFRED KRANES What was the source of the pulmonary emboli?

DR CASTLEMAN I suppose from the leg veins. We were unable to examine them, but we know that there was a phlebitis clinically.

DR CHAPMAN Could they not have come from the right auricle?

DR CASTLEMAN No, there was no mural thrombus in the right. There is the possibility that atherosclerosis of the pulmonary arteries, which occurs with mitral stenosis, may have initiated the formation of small thrombi. I have always believed, however, that pulmonary thrombosis rarely occurs and that most of the lesions in the pulmonary circuit are emboli rather than local thrombi.

CASE 35382

PRESENTATION OF CASE

A seventy-five-year-old nulliparous widow was admitted to the hospital because of vomiting and abdominal pain.

In the two years prior to admission the patient had been "below par" and had lost 25 pounds. For one year she had had progressive constipation, passing small, hard stools occasionally mixed with blood. Two days before admission she noted obstipation, cramping lower abdominal pain and vomiting of all ingested material. There was no fecal return from several enemas, and various laxatives taken were vomited.

The past history included a right radical mastectomy for carcinoma twenty years previously and a total hysterectomy and salpingo-oophorectomy for cancer of the uterine fundus twelve years before admission. The appendix was said not to have been removed. The patient had noted anginal chest pain on exertion for five years, with occasional nocturnal dyspnea, and had been taking digitalis up to one month prior to admission.

Physical examination showed a dehydrated, elderly woman. The heart was enlarged to percussion. A rough systolic murmur transmitted into the neck was heard in the aortic area, and there were systolic and presystolic murmurs at the apex. The abdomen was distended, somewhat rigid, and showed rebound tenderness referred to both lower quadrants. There was tenderness in both vaginal vaults and some fullness more on the right. An indistinctly outlined mass was felt in the right lower quadrant.

The temperature was 102°F, the pulse 100, and the respirations 24. The blood pressure was 110 systolic, 70 diastolic.

pattern is very characteristic I think cor pulmonale, congenital heart disease and mitral stenosis are the most likely possibilities

May we see the x-ray films? The earlier films might have been helpful, but we do not have them. Do you see anything that suggests long-standing pulmonary disease or congestion on a vascular basis?

DR STANLEY M WYMAN The pattern in the lung shows first of all enlarged hilar shadows. I take them to be engorged vessels. The peripheral vascular findings and the fluid in the right pleural space and probably to a slight degree in the left, perhaps in an interlobar fissure, suggest pulmonary congestion and cardiac decompensation. I cannot say whether these peripheral nodular changes are acute or chronic on this one film, but they disappear later except for a few small nodules that remain out in the periphery of the left lung.

DR WILLIAMS Do you wish to comment on the possibility of mitral stenosis?

DR WYMAN I think the films are good evidence for an enlarged left auricle seen through the heart. These two films outline the left main bronchus and form a double contour as seen on the right of the heart. That is also seen to some degree on the lateral projection. I cannot comment on the ventricular enlargement, but it could be left or right.

DR WILLIAMS Do you think the prominence of the pulmonary artery would account for that?

DR WYMAN I do not believe it could account for all of it, surely, it could not give a double contour of the auricle through the heart.

DR WILLIAMS Apparently this picture gradually subsided.

The mid-diastolic murmur is, of course, helpful in the diagnosis of mitral stenosis. On the other hand, it is well to recall that ventricular dilatation alone may produce a mid-diastolic rumble. The patient had auricular fibrillation, so no presystolic murmur could be heard. "Auricular fibrillation was present at each examination." This recurring statement is quite important.

The tender swelling in the leg three months before admission may have been important, and made me wonder whether pulmonary embolism, which is a common complication in a history of this kind, had at last appeared.

The positive guaiac reaction made me wonder whether the patient had been swallowing bloody sputum or whether he had had a mesenteric embolus secondary to long-standing auricular fibrillation. It is evident from the repeated blood cultures that the diagnosis of subacute bacterial endocarditis was entertained at this time, but no evidence for it was found. I think it is likely that the low-salt diet accounted in this case for weakness as it does in so many others.

Anorexia may have been due to the distended liver or some lesion in the abdomen such as a mesenteric lesion.

To sum up rapidly, I am quite sure that this patient had mitral stenosis, whatever else he may have

had. I probably feel that way because of the early onset and persistence of auricular fibrillation in a man of forty-two at the time of the first hospital admission. Also, the x-ray pictures and the electrocardiogram are both in keeping. However, I do not believe that mitral stenosis accounts for everything.

At autopsy, I should not be surprised to find evidence of chronic bronchial disease or emphysema or possibly pulmonary fibrosis. Did he have subacute bacterial endocarditis? It is possible that he did. There was a history of teeth extractions, although they were covered by penicillin in each instance.

One other thing we ought to consider in a patient who has had peripheral venous congestion so long is constrictive pericarditis. Among many objections to this diagnosis is the proportion of dyspnea to other symptoms. It is true that many patients with constrictive pericarditis also have dyspnea but certainly not to this extent, nor are they troubled by cough as this patient was.

So for my principal diagnosis, I will say that this man had mitral stenosis, with rheumatic heart disease, and chronic bronchitis. I disregard the possibility of congenital heart disease because right-axis deviation in the absence of cyanosis does not fit in with the x-ray picture. It is remotely conceivable that he had auricular septal defect, but I doubt it. We have seen an occasional case of patent ductus arteriosus with nothing but a mitral rumble and without the usual characteristic murmurs. However, I dismiss this possibility. I considered the possibility of amyloidosis to account for the renal picture, which somewhat approaches that of the nephrotic syndrome. This does remain a possibility. I cannot very well account for it on any other grounds. I do not believe he had chronic nephritis. He maintained a good urine concentration throughout the illness. Many cases discussed at these conferences turn up with unexpected acute glomerulonephritis at autopsy, but there is no evidence for it here.

DR HOWARD B SPRAGUE You have to include the possibility of reactivation of rheumatic fever, do you not?

DR WILLIAMS I meant to mention it. I should not be surprised to find Aschoff bodies in the myocardium. It is quite possible that the patient died in active rheumatic fever.

DR EARLE M CHAPMAN Would you include the possibility of pulmonary infarction?

DR WILLIAMS No, but I would not be surprised to find small pulmonary emboli at autopsy.

DR SPRAGUE I saw the patient on his original entry and for some time followed him in the Out-Patient Department. The problem was considered to be cor pulmonale. I turned him on his side one day and found that he had a sharp aortic first sound and a mitral diastolic rumble. I am on record as saying that he had mitral stenosis, so I will stand or fall on that.

cardiac mural thrombus was thrown off to the mesenteric artery. She could have had thrombosis on the venous side, with infarction of a small area of bowel. It is conceivable that this could produce a temporary intestinal obstruction, that the viability of that part of the bowel would be in doubt for some days and then that circulation would be re-established by way of collateral vessels later. Then, perhaps, on the sixteenth day in the hospital a fresh venous thrombus occurred, possibly a massive thrombosis of the mesenteric or even the portal vein caused the vomiting of fresh blood and the passing of blood by rectum. In fact, a high thrombosis of the mesenteric vein is the only way I can explain bleeding from both the upper and the lower intestinal tract, so I am going to make this my diagnosis.

I might say something about the prothrombin time. It was 48 per cent of normal on admission. That suggests one of two things to me: liver disease or malnutrition. There is nothing in the protocol that suggests liver disease so I am going to say it was due to malnutrition. It is not at all uncommon for a woman or man over seventy to lose weight, to lose appetite and stop eating and to become chronically dehydrated. This may be the explanation for the weight loss and constipation, rather than a chronic malignant lesion of the bowel.

DR JOHN W RAKER: When this woman came into the Emergency Ward most of the people who saw her preferred a diagnosis of perforated appendix, with appendiceal abscess. We called the hospital where she was operated on previously, and it was definitely ascertained that the appendix was left behind according to the hospital record. It was our opinion at the time of admission that she was too ill to stand an operation, although there was considerable discussion about it. We thought she had a certain amount of congestive failure as well as dehydration. There was evidence that something was localizing in the right lower quadrant. We followed her on a conservative regime for five days and began to think that we might drain her through the right lower quadrant. The symptoms subsided spontaneously with the appearance of foul stools, and we thought perhaps she had drained herself into the bowel. We waited in the hope that we could reach the stage where we could safely operate on her. The electrocardiogram showed the findings recorded. We were never able to explain why she was bleeding, although we persisted to the end in our belief that she probably had a perforated appendix.

DR TRACY B MALLORY: There must have been some consideration of carcinoma of the cecum because that was the written diagnosis on the death report.

DR RAKER: I believe the majority of people who saw her favored the diagnosis of appendiceal abscess. There was a minority in favor of carcinoma of the cecum, and the doctor who signed the death report must have belonged to that minority.

CLINICAL DIAGNOSIS

Appendiceal abscess?

Carcinoma of cecum?

DR HARWOOD'S DIAGNOSIS

Mesenteric thrombosis

ANATOMICAL DIAGNOSES

Abdominal abscess

Generalized peritonitis

Jejunioileal fistula

Anterior myocardial infarct, recent

Duodenal ulcers, active

Aneurysm of descending aorta

PATHOLOGICAL DISCUSSION

DR MALLORY: The autopsy findings were rather puzzling, and I do not feel entirely satisfied that we can explain everything we found. She had a large intra-abdominal abscess, and the stump of the appendix projected into this abscess. It was only 1 cm in length and was densely fibrous and had no lumen. It would be rather unusual for an appendix of that type—that is, an obliterated appendix—to perforate, and we could find nothing that we could recognize as necrotic portions of the appendix. As the autopsy was continued we found that there was a fistulous tract between the jejunum, about 20 cm below the ligament of Treitz, and one of the lower loops of the ileum, and this fistula was in immediate approximation with the intra-abdominal abscess, so that leakage could have occurred through that. The walls of the fistula were slightly inflamed and thickened. There was no evidence of neoplasm, tuberculosis or any specific infection. The origin and nature of that lesion, I cannot explain. How long this fistula had been present, we are unable to say, and whether it or the appendix was the source of the abdominal abscess also has to remain a doubtful question.

She also had a severe arteriosclerotic heart disease, with numerous spots of marked narrowing of the left descending coronary artery and a focus of fresh infarction, a little over 2 cm in diameter, in the interventricular septum. An incidental finding was an arteriosclerotic aneurysm of the abdominal aorta containing a mural thrombus.

DR RAKER: Was not something found in the duodenum?

DR MALLORY: There were two acute peptic ulcers in the duodenum that accounted for the vomiting of blood. We did explain that.

A PHYSICIAN: Another possibility to explain that bleeding is acute pancreatitis.

DR MALLORY: The pancreas showed only interstitial edema, such as one commonly sees in a case with peritoneal infection.

A PHYSICIAN: Was there dissection in the aneurysm?

DR MALLORY: No, it was a simple pouch-like arteriosclerotic aneurysm.

Laboratory studies showed a normal urine. The hemoglobin was 13.5 gm per 100 cc, and the white-cell count was 12,950. The stools gave a ++ guaiac reaction on two occasions. The nonprotein nitrogen was 44 mg, and the total protein 6.3 gm per 100 cc, the serum chloride 104 milliequiv per liter, and the prothrombin time 48 per cent of normal. Vaginal smears showed no neoplastic cells. Plain films of the abdomen showed gas-filled loops of small and large bowel. Chest x-ray films confirmed the cardiac enlargement.

A Miller-Abbott tube was inserted, and a transfusion of 500 cc of whole blood administered. The patient was started on intravenous injection of fluids, penicillin, streptomycin, Digalen and opiates. Peristalsis was audible, and she occasionally passed gas by rectum. However the temperature and white-cell count remained elevated and the urinary output was very low. On the seventh day the pulse rate rose to 210, and an electrocardiogram showed auriculoventricular dissociation. Tachycardia was incompletely controlled by quinidine. The right-lower-quadrant mass seemed to decrease in size, as did a fullness in the right vault on the eighth day, when foul, liquid bowel movements began. Active normal peristalsis was heard at this time, and for five days she tolerated liquids by mouth with the Miller-Abbott tube out. On the sixteenth day she began to vomit fresh blood and coffee-grounds material and to pass fresh clots by rectum. The blood pressure fell to 80 systolic, 60 diastolic, and the patient complained of anginal pain.

Transfusion of 1000 cc of whole blood produced some clinical improvement, but on the morning of the eighteenth day she suddenly became disoriented, the heart beat and respirations ceased, and she was pronounced dead.

DIFFERENTIAL DIAGNOSIS

DR REED HARWOOD: May we see the x-ray films?

DR JAMES A. McCORT: The x-ray examination was limited to a plain film of the abdomen. The tip of a Miller-Abbott tube is present in the fundus of the stomach. Distal to the stomach there are at least two dilated loops of small bowel. Air is present in the ascending colon. There may also be a small amount of air in the descending colon and sigmoid. The mass described in the protocol is not visible on the x-ray film.

DR HARWOOD: Is that a pressure defect?

DR McCORT: There is not a sufficient amount of air in the cecum for me to be certain.

DR HARWOOD: The history, then, is one of intestinal obstruction that relieved itself after eight days in the hospital. Ten days later the patient vomited fresh blood and also passed fresh blood by rectum and rapidly went into shock and died.

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We know from previous exercises that it is not at all uncommon for a patient to have two or three carcinomas in different organs of the body. Perhaps this patient had a predisposition for the formation of malignant tumors. The history is good for carcinoma of the bowel. She had chronic constipation and a down-hill course for over a period of two years, with increasing constipation, finally ending in obstruction. The physical findings are consistent with such a diagnosis. We know with carcinoma of the right colon that the typical history is alternating periods of constipation and diarrhea, but there is no suggestion that she had diarrhea in the past two years. The obstruction was relieved in this case, and I should not expect that to occur in carcinoma that has slowly encircled the lumen of the cecum or ascending colon. Tumor of the ileum with intussusception and intussusception from a tumor in the region of the cecum are both possibilities that are attractive because of the fact that after eight days in the hospital the obstruction was relieved and she passed foul, liquid bowel movements. I would rather expect this patient to have been much sicker, possibly in shock, with a much higher white-cell count if she had had intussusception on admission.

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Finally, we come to a consideration of mesenteric thrombosis, venous or arterial. If arterial, it could have been the result of arteriosclerosis of the mesenteric arteries or an embolus from some other source. We know, for example, that the patient had arteriosclerotic heart disease, and it is possible, although I think unlikely, that she had had a coronary occlusion in the recent past and an embolus from a

cardiac mural thrombus was thrown off to the mesenteric artery. She could have had thrombosis on the venous side, with infarction of a small area of bowel. It is conceivable that this could produce a temporary intestinal obstruction, that the viability of that part of the bowel would be in doubt for some days and then that circulation would be re-established by way of collateral vessels later. Then, perhaps on the sixteenth day in the hospital a fresh venous thrombus occurred, possibly a massive thrombosis of the mesenteric or even the portal vein caused the vomiting of fresh blood and the passing of blood by rectum. In fact, a high thrombosis of the mesenteric vein is the only way I can explain bleeding from both the upper and the lower intestinal tract, so I am going to make this my diagnosis.

I might say something about the prothrombin time. It was 48 per cent of normal on admission. That suggests one of two things to me: liver disease or malnutrition. There is nothing in the protocol that suggests liver disease so I am going to say it was due to malnutrition. It is not at all uncommon for a woman or man over seventy to lose weight, to lose appetite and stop eating and to become chronically dehydrated. This may be the explanation for the weight loss and constipation, rather than a chronic malignant lesion of the bowel.

DR JOHN W. RAKER: When this woman came into the Emergency Ward most of the people who saw her preferred a diagnosis of perforated appendix, with appendiceal abscess. We called the hospital where she was operated on previously, and it was definitely ascertained that the appendix was left behind according to the hospital record. It was our opinion at the time of admission that she was too ill to stand an operation, although there was considerable discussion about it. We thought she had a certain amount of congestive failure as well as dehydration. There was evidence that something was localizing in the right lower quadrant. We followed her on a conservative regime for five days and began to think that we might drain her through the right lower quadrant. The symptoms subsided spontaneously with the appearance of foul stools, and we thought perhaps she had drained herself into the bowel. We waited in the hope that we could reach the stage where we could safely operate on her. The electrocardiogram showed the findings recorded. We were never able to explain why she was bleeding, although we persisted to the end in our belief that she probably had a perforated appendix.

DR TRACY B. MALLORY: There must have been some consideration of carcinoma of the cecum because that was the written diagnosis on the death report.

DR RAKER: I believe the majority of people who saw her favored the diagnosis of appendiceal abscess. There was a minority in favor of carcinoma of the cecum, and the doctor who signed the death report must have belonged to that minority.

CLINICAL DIAGNOSIS

Appendiceal abscess?
Carcinoma of cecum?

DR HARWOOD'S DIAGNOSIS

Mesenteric thrombosis

ANATOMICAL DIAGNOSES

Abdominal abscess
Generalized peritonitis
Jejunioileal fistula
Anterior myocardial infarct, recent
Duodenal ulcers, active
Aneurysm of descending aorta

PATHOLOGICAL DISCUSSION

DR MALLORY: The autopsy findings were rather puzzling, and I do not feel entirely satisfied that we can explain everything we found. She had a large intra-abdominal abscess, and the stump of the appendix projected into this abscess. It was only 1 cm. in length and was densely fibrous and had no lumen. It would be rather unusual for an appendix of that type—that is, an obliterated appendix—to perforate, and we could find nothing that we could recognize as necrotic portions of the appendix. As the autopsy was continued we found that there was a fistulous tract between the jejunum, about 20 cm. below the ligament of Treitz, and one of the lower loops of the ileum, and this fistula was in immediate approximation with the intra-abdominal abscess, so that leakage could have occurred through that. The walls of the fistula were slightly inflamed and thickened. There was no evidence of neoplasm, tuberculosis or any specific infection. The origin and nature of that lesion, I cannot explain. How long this fistula had been present, we are unable to say, and whether it or the appendix was the source of the abdominal abscess also has to remain a doubtful question.

She also had a severe arteriosclerotic heart disease, with numerous spots of marked narrowing of the left descending coronary artery and a focus of fresh infarction, a little over 2 cm. in diameter, in the interventricular septum. An incidental finding was an arteriosclerotic aneurysm of the abdominal aorta containing a mural thrombus.

DR RAKER: Was not something found in the duodenum?

DR MALLORY: There were two acute peptic ulcers in the duodenum that accounted for the vomiting of blood. We did explain that.

A PHYSICIAN: Another possibility to explain that bleeding is acute pancreatitis.

DR MALLORY: The pancreas showed only interstitial edema, such as one commonly sees in a case with peritoneal infection.

A PHYSICIAN: Was there dissection in the aneurysm?

DR MALLORY: No, it was a simple pouch-like arteriosclerotic aneurysm.

Laboratory studies showed a normal urine. The hemoglobin was 13.5 gm per 100 cc, and the white-cell count was 12,950. The stools gave a ++ guaiac reaction on two occasions. The nonprotein nitrogen was 44 mg, and the total protein 6.3 gm per 100 cc, the serum chloride 104 milliequiv per liter, and the prothrombin time 48 per cent of normal. Vaginal smears showed no neoplastic cells. Plain films of the abdomen showed gas-filled loops of small and large bowel. Chest x-ray films confirmed the cardiac enlargement.

A Miller-Abbott tube was inserted, and a transfusion of 500 cc of whole blood administered. The patient was started on intravenous injection of fluids, penicillin, streptomycin, Digalen and opiates. Peristalsis was audible, and she occasionally passed gas by rectum. However the temperature and white-cell count remained elevated and the urinary output was very low. On the seventh day the pulse rate rose to 210, and an electrocardiogram showed auriculoventricular dissociation. Tachycardia was incompletely controlled by quinidine. The right-lower-quadrant mass seemed to decrease in size, as did a fullness in the right vault on the eighth day, when foul, liquid bowel movements began. Active normal peristalsis was heard at this time, and for five days she tolerated liquids by mouth with the Miller-Abbott tube out. On the sixteenth day she began to vomit fresh blood and coffee-ground material and to pass fresh clots by rectum. The blood pressure fell to 80 systolic, 60 diastolic, and the patient complained of anginal pain.

Transfusion of 1000 cc of whole blood produced some clinical improvement, but on the morning of the eighteenth day she suddenly became disoriented, the heart beat and respirations ceased, and she was pronounced dead.

DIFFERENTIAL DIAGNOSIS

DR REED HARWOOD: May we see the x-ray films?

DR JAMES A. McCORT: The x-ray examination was limited to a plain film of the abdomen. The tip of a Miller-Abbott tube is present in the fundus of the stomach. Distal to the stomach there are at least two dilated loops of small bowel. Air is present in the ascending colon. There may also be a small amount of air in the descending colon and sigmoid. The mass described in the protocol is not visible on the x-ray film.

DR HARWOOD: Is that a pressure defect?

DR McCORT: There is not a sufficient amount of air in the cecum for me to be certain.

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type of study that Gordon has so successfully developed

REFERENCES

1. Gordon J. E. Home accidents as community health problem. *Am J M Sc* 217:323-344 1949
2. *Idem*. Epidemiology of accidents. *Am J Pub Health* 39:504-515 1949

PEDIATRIC SURVEY

THE nationwide study of health services for children conducted by the American Academy of Pediatrics during the past three years, state by state, has been published by the Commonwealth Fund and reviewed in the *Journal* of September 8. In the current issue can be found a brief but explicit summary of the report on the Massachusetts survey.

Wholly aside from the statewide study, Massachusetts appears to have figured prominently in the national picture. Dr Warren R Sisson, of Boston, was chairman of the Committee for the Study of Child Health Services when the pilot study in North Carolina was undertaken in 1945, and is currently president of the Academy as the reports are being issued. Dr John P Hubbard, also *loc cit*, has been executive director of the entire survey from its inception.

The study has been decentralized to an unusual degree, each state chairman having been required to develop his own organization, plan the financing of the work and arrange for the publication of the findings. The report on the Massachusetts Survey is published by the American Academy of Arts and Sciences.

In general, throughout the state surveys, data have been tabulated by counties and by the metropolitan character of counties, a classification that depends on both population density and proximity to centers of population. Only three of the fourteen counties of Massachusetts — Barnstable, Dukes and Nantucket, are classed as "isolated," and it has been found practical in this state to utilize the public-health districts in preference to county divisions.

Certain not altogether palatable data have been brought out by the survey. Massachusetts is the twelfth wealthiest state in the Union but ranks twenty-second in maternal and twentieth in infant

mortality. Boston in particular has an infant-mortality rate one point higher than the national average, despite the fact that the Commonwealth ranks third among the states with respect to the total amount of medical service that its children receive, and second with respect to the number of practicing physicians in relation to population. It ranks fifth with respect to the number of dentists in practice.

The training of physicians and dentists in the specialized care of children has been found on the whole to be deficient, the average general practitioner requiring more pediatric training both in medical school and in the hospital than he is now receiving.

The distribution and utilization of pediatric hospital beds is uneven, a prime need in the field of chronic care being for more beds for mentally deficient and epileptic patients. A program for graduate pediatric education is desirable, this could be sponsored by the Massachusetts Medical Society, the New England Pediatric Society and the Massachusetts Chapter of the American Academy of Pediatrics.

Criticism in any field of endeavor is of value in direct relation to the available knowledge on which it is based. The work that Baty and Snedeker have done in Massachusetts in straight fact-finding, which can be multiplied by the number of states in the union, is impressive. It is now the responsibility of the medical profession and of the public to convert this information into an active program.

The channels through which medical service flows and the methods by which it becomes available may change from generation to generation and may be often the subject of debate. The obligation of the profession to provide the best service possible to all who need it never changes.

PUBLIC HEALTH AND PRIVATE PRACTICE

DR HENRY I BOWDITCH, of Boston, — then chairman of the Massachusetts State Board of Health, — enunciated the following principle in the Centennial Discourse on Public Hygiene delivered at the Philadelphia Exposition in 1876:

Still further I hold it to be true that the study of the prevention of disease is the only branch of medical learning

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EPIDEMIOLOGY OF TRAUMA

ONLY a study of all the factors that affect health can lead to an intelligent program for its preservation. In the field of trauma, as Gordon¹ has previously pointed out, any organized approach to the problem of accidents, occurring singly or in catastrophic numbers, was originally centered on relief. It was for relief that the Red Cross was organized—first for the relief of stricken soldiers, then, under the American Amendment, for the relief of civilians in time of disaster. Not until later did the idea of prevention begin to prevail, and then it was advanced mainly by industry.

Elsewhere the same author² has indicated the growth of the concept of the epidemiologic method from its original restriction to the communicable diseases to a broader application to the other afflictions of mankind as well as including such conditions as cancer and diabetes and even the con-

genital malformations. Epidemiology, as a study of cause and effect in their relation to health, can be equally well applied to an investigation of the traumatic hazards.

These possibilities can be variously illustrated by analyses of "point" epidemics, representing "that circumstance where a sharp aggregation of cases occurs within a brief interval as the result of a single agent acting during a prescribed and limited time." In this category is the explosive eruption of typhoid-fever cases two weeks after a circus train inadvertently filled its tanks from a standpipe delivering untreated river water. The accidental deaths occurring as a result of the Coconut Grove fire in Boston in 1942 were in the same class, as was the outbreak of trench foot in an infantry division following the Battle of the Bulge.

Three factors, or some combination of the three, are involved when the "established and satisfactory equilibrium or adjustment between man and his environment" that is called health is disturbed. These are the direct causative factor or agent, the environmental factor, and the host factor.

A study of them all is important if a practical program of control is to be worked out. Not only can the epidemiology of accidents be analyzed in the same manner as that of disease, but practical preventive measures will result from a survey of the causative factors.

In this issue of the *Journal* Roberts and Gordon present an investigation into the epidemiology of home accidents as they occur in Massachusetts. The Massachusetts accident death rate is lower than that for the country as a whole, but the Commonwealth's low automobile death rate is responsible. Fatal home accidents are actually proportionately more important in Massachusetts than in the nation.

Not only do the authors present a statistical analysis of the local status, but advice regarding the studies on which efficient control methods can be based.

In respect to the epidemiology of trauma it is interesting to note that considerable attention is now being focused on accidents occurring on the farm. Here, where a high rate of unnecessary mishaps is being reported, is a fruitful field for the

A firm in New York say that they have received a specimen of reputed cod-liver oil from Boston, that does not contain a particle of that article!—It is asserted, on the authority of Mr Fairchild, that seven hundred drunkards die annually in the sober state of Connecticut

Married,—Dr Hardenbrook, of Rochester N Y, to Mrs Nott He has been tried and acquitted of poisoning her husband

Boston M & S J, September 19, 1849

OBITUARY

FREDERIC AUGUSTUS WASHBURN

1869-1949

Dr Frederic Augustus Washburn, former director of the Massachusetts General Hospital, died on August 20, 1949. He had served as director of the hospital from 1908 until his retirement in 1934.

Dr Washburn was born in New Bedford in 1869. He graduated from Amherst College in 1892 and received his medical degree from Harvard Medical School four years later. His service at the Massachusetts General Hospital began in 1897, when he was appointed house officer on the South Surgical Service. He became director of the Massachusetts Eye and Ear Infirmary in 1915.

He was surgeon and first lieutenant with the Sixth Massachusetts Volunteers in the Porto Rico Campaign (1898-99), assistant surgeon and captain with the Twenty-Sixth U S Volunteers in the Philippines (1899-1903) and major and colonel in World War I, during which he organized and commanded Base Hospital No 6, later he was in charge of all United States Army hospitals in Great Britain, receiving the Distinguished Service Medal and the orders of St Michael and St George.

In 1930 Dr Washburn founded the Baker Memorial Hospital for the care of people of moderate means, with hospital charges at cost and a limited professional fee. After his retirement he was appointed Commissioner of Institutions for the city of Boston. From 1937 to 1946 he was director of the Cambridge Hospital (now the Mount Auburn Hospital).

He was a former president of the American Hospital Association and was a fellow of the American Medical Association.

Dr Washburn was noted for his ability as an administrator as well as for the charm of his personality. He will be greatly missed by all those with whom he was associated, both in his professional capacity and as a friend.

N W F

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

BAKER—Benjamin W Baker, M D, of Laconia, died on August 17. He was in his seventy-sixth year.

Dr Baker received his degree from Dartmouth Medical School in 1898. He was formerly medical director and superintendent of the Laconia State School and was a member of the New England Society of Psychiatry and the American Psychiatric Association and a fellow of the American Medical Association.

His widow, a daughter and a brother survive.

WEAVER—George A Weaver, M D, of Bradford, Vermont, died on June 22. He was in his eighty-first year.

Dr Weaver received his degree from Yale University School of Medicine in 1897. He was a fellow of the American Medical Association, and on June 15, 1949, had received a medal commemorating his fifty years' membership in the New Hampshire Medical Society.

His widow, a son, a daughter, two grandchildren and a sister survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The October schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Salem	October 3	Paul W. Hugenberger
Haverhill	October 5	William T. Green
Lowell	October 7	Albert H. Brewster
Greenfield	October 10	Charles L. Sturdevant
Gardner	October 11	Carter R. Rowe
Brockton	October 13	George W. Van Gorder
Springfield	October 18	Garry deN. Hough, Jr
Pittsfield	October 19	Frank A. Slowick
Worcester	October 21	John W. O'Meara
Fall River	October 24	David S. Grice
Hyannis	October 27	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Reproduction and Survival. By R. Christie Brown, M B, M S, F R C S, F R C O G, obstetric surgeon, City of London Maternity Hospital, honorary surgeon, Samaritan Free Hospital for Women, and gynecologist, Metropolitan Hospital 12, cloth, 108 pp. London: Edward Arnold and Company, 1948. \$2.25.

Psychiatry, A short treatise. By William A. O'Connor, L M S S A (Lond.), D P M (Lond.), medical superintendent, Ashwood House, Kinswinford, Staffs., and tutor (psychology) of extra-mural, University, and W E A classes 8, cloth, 380 pp. Baltimore: Williams and Wilkins Company, 1948. \$9.00.

Conditioned Reflexes and Neuron Organization. By Jerzy Konorski, head of the Department of Neurophysiology in the Nencki Institute of Experimental Biology, and professor in the University of Lodz. Translated from the Polish manuscript under the author's supervision by Stephen Garry 8, cloth, 267 pp., with 18 illustrations. Cambridge: University Press, New York: Macmillan Company, 1948. \$4.00 (Cambridge Biological Studies).

which the State can legitimately undertake. The practice of medicine and surgery and the appropriate use of drugs, must be left to medical schools and to private practitioners of medicine. The State, as a student of the causes of all disease, only supplements, and indeed nobly supplements them.*

In those days, too, there were giants in the earth.

Aside from the present aims and future goals of state and federal Government in relation to health and disease, it is obvious that considerably more oversight of health in general is being exercised in 1949 than was the case in 1876. Nor is all of this paternalistic solicitude to be condemned. Public health and private practice when each is properly conducted have but one common goal and, when each is conducted properly, that goal can be approached with mutual harmony and consideration.

Even Dr. Bowditch, amazed as he might be at group health insurance and shocked as he certainly would be at the current efforts of Government to introduce compulsory health insurance, would nevertheless have considered it a proper function of the State to care for its military personnel, its veterans (to a degree) and its indigent. He, too, would have believed it to be a function of public health to co-operate with the private practitioner, and would have expected the practitioner on his part to co-ordinate his efforts with those of public health, and to reap its benefits. Certainly the physician who today opposes this policy must accept the burden of proving that he is right in doing so.

It is this capacity of public and private service for working together that has been ably demonstrated in the public-health heart program instituted a year ago in Newton, Massachusetts, and reported elsewhere in this issue of the *Journal*.

This program, conceived as a pilot study of the public-health aspects of heart disease was endorsed by the Massachusetts Medical Society in May, 1948, and activated under the joint sponsorship of the Newton Health Department, the Massachusetts Department of Public Health and the United States Public Health Service. Its objectives are "to determine methods of helping to reduce cardiovascular disease and conserve cardiac

function", its program is based on the belief that heart disease constitutes a public-health problem, and that public-health measures will yield results in its control. It early received the endorsement of the Newton Medical Club and has progressed to the point of its present report through the co-operation of the practicing profession.

MEDICAL ILLUSTRATION

AN ESSENTIAL part of medical publication is adequate illustration. The point of an article is often made quite as much by an expert drawing of a part of the body or a carefully worked out diagram as by a description in words, indeed, a clear, professionally presented illustration is occasionally of more value than paragraphs of text.

Those who write for publication in medical journals will therefore be interested in the fourth annual convention of the Association of Medical Illustrators, which will be held in Boston from October 3 through October 6. Founded in 1946, the Association is dedicated to the following purpose: "to advance medical education and to promote understanding and co-operation with the medical and related professions."

The program of the convention includes talks by members of the Association on the administration of their departments, with discussions led by Dr. Joseph S. Lichty, an exhibition of work by members, an address by Dr. Robert M. Green and meetings in the Ether Dome of the Massachusetts General Hospital, with a demonstration of air-brush technique, a description of a new "Colotone" printing process and a lecture on the use of plastic materials. Of particular interest is the memorial lecture, delivered by Dr. Reginald Fitz, which commemorates the work of Max Brodell, who for thirty years conducted the Department of Art as Applied to Medicine at Johns Hopkins University School of Medicine and under whom many members of the Association studied.

It is hoped that the convention of specialists in what may be considered an adjunct to medical science will be as successful and informative as the meetings held in previous years in Philadelphia, New Orleans and Chicago.

*Emerson H. Whither the Pegasus of public health? Cutter Lecture on Preventive Medicine. *New Eng J Med* 238: 679-687, 1948.

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COMBINED MEDICAL AND SURGICAL MANAGEMENT OF UPPER GASTROINTESTINAL HEMORRHAGE*

THOMAS A. WARTHIN, M.D.,† RICHARD WARREN, M.D.,‡ AND EGON G. WISSING, M.D.§

WEST ROXBURY, MASSACHUSETTS

MANY excellent reviews of the problems in management of upper gastrointestinal bleeding have been presented by various internists and surgeons. Almost without exception the material has been analyzed from the point of view of the internist or the surgeon. Rarely has the combined approach been presented, although recent papers by Jones,¹ Heuer,² Schatzki³ and Hoerr⁴ have emphasized this. It is our purpose to demonstrate that the most efficient way to deal with massive bleeding is by means of a combined medical and surgical team in conjunction with a well trained roentgenologist. In the Veterans Administration Hospital, West Roxbury, such a team has been in existence during the past two and a half years.

MATERIAL

Although a combined medical and surgical responsibility in the therapy of upper gastrointestinal bleeding is most applicable when the source of hemorrhage is a peptic ulcer, the matter of diagnosis is so implicated with that of treatment that such a team must inevitably consider in some degree all causes of the hemorrhage. During the period from July 1, 1946, to June 30, 1948, 10,342 patients were admitted to the hospital, of whom 181 had upper gastrointestinal bleeding as their primary complaint. It has been convenient to divide these patients into three groups — massive, intermediate and slight — according to the severity of the hemorrhage. The massive group was composed of 86 patients and included those in whom the red-cell count fell below 3,000,000. The intermediate group, in which hemorrhage was sufficient to effect a fall in the red-cell count to less than 4,000,000 but

greater than 3,000,000, contained 50 patients. In addition, 45 cases of slight hemorrhage occurred in which the red-cell count did not fall below 4,000,000. Of total hospital admissions 1.7 per cent were for upper gastrointestinal bleeding, 0.8 per cent being for massive hemorrhage. During the same period 494 patients with simple or complicated peptic ulcer were admitted to the hospital, 117, or 23 per cent, for hemorrhage. Of the 86 cases of massive hemorrhage 56, or 65 per cent, were demonstrated to be due to peptic ulceration, whereas the remaining 30 were due to esophageal varices, gastritis or undetermined conditions. Table 1 illustrates the dispersion of the cases according to source of the hemorrhage, the various diagnoses listed in the cases without ulcer are similar to those observed in other clinics (Hoerr⁴ and Stolte⁵). It is of interest that in 15 per cent of the patients no site of origin of the hemorrhage could be demonstrated, and that in only 3 of these 14 patients could a history suggestive of ulcer be obtained. Reports from other clinics also contain a seemingly irreducible number of patients who must be put in this undiagnosed group. The origin of their hemorrhages will probably always remain obscure.

In 65 per cent of patients admitted for massive upper gastrointestinal bleeding the source was demonstrated to be a peptic ulceration. Among this group 85.7 per cent of cases were due to duodenal ulcer, 12.6 per cent to gastric ulcer, and 1.7 per cent to marginal ulcer. The ratio of these three types of ulcers to each other is comparable with that found in any group of ulcers whether bleeding or not. In the intermediate and slight groups a similar ratio of bleeding due to ulcer and other conditions was obtained.

MORTALITY

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COMBINED MEDICAL AND SURGICAL MANAGEMENT OF UPPER GASTROINTESTINAL HEMORRHAGE*

THOMAS A. WARTHIN, M.D.,† RICHARD WARREN, M.D.,‡ AND EGON G. WISSING, M.D.§

WEST ROXBURY, MASSACHUSETTS

MANY excellent reviews of the problems in management of upper gastrointestinal bleeding have been presented by various internists and surgeons. Almost without exception the material has been analyzed from the point of view of the internist or the surgeon. Rarely has the combined approach been presented, although recent papers by Jones,¹ Heuer,² Schatzki³ and Hoerr⁴ have emphasized this. It is our purpose to demonstrate that the most efficient way to deal with massive bleeding is by means of a combined medical and surgical team in conjunction with a well trained roentgenologist. In the Veterans Administration Hospital, West Roxbury, such a team has been in existence during the past two and a half years.

MATERIAL

Although a combined medical and surgical responsibility in the therapy of upper gastrointestinal bleeding is most applicable when the source of hemorrhage is a peptic ulcer, the matter of diagnosis is so implicated with that of treatment that such a team must inevitably consider in some degree all causes of the hemorrhage. During the period from July 1, 1946, to June 30, 1948, 10,342 patients were admitted to the hospital, of whom 181 had upper gastrointestinal bleeding as their primary complaint. It has been convenient to divide these patients into three groups — massive, intermediate and slight — according to the severity of the hemorrhage. The massive group was composed of 86 patients and included those in whom the red-cell count fell below 3,000,000. The intermediate group, in which hemorrhage was sufficient to effect a fall in the red-cell count to less than 4,000,000 but

greater than 3,000,000, contained 50 patients. In addition, 45 cases of slight hemorrhage occurred in which the red-cell count did not fall below 4,000,000. Of total hospital admissions 1.7 per cent were for upper gastrointestinal bleeding, 0.8 per cent being for massive hemorrhage. During the same period 494 patients with simple or complicated peptic ulcer were admitted to the hospital, 117, or 23 per cent, for hemorrhage. Of the 86 cases of massive hemorrhage 56, or 65 per cent, were demonstrated to be due to peptic ulceration, whereas the remaining 30 were due to esophageal varices, gastritis or undetermined conditions. Table 1 illustrates the dispersion of the cases according to source of the hemorrhage, the various diagnoses listed in the cases without ulcer are similar to those observed in other clinics (Hoerr⁴ and Stolte⁵). It is of interest that in 15 per cent of the patients no site of origin of the hemorrhage could be demonstrated, and that in only 3 of these 14 patients could a history suggestive of ulcer be obtained. Reports from other clinics also contain a seemingly irreducible number of patients who must be put in this undiagnosed group. The origin of their hemorrhages will probably always remain obscure.

In 65 per cent of patients admitted for massive upper gastrointestinal bleeding the source was demonstrated to be a peptic ulceration. Among this group 85.7 per cent of cases were due to duodenal ulcer, 12.6 per cent to gastric ulcer, and 1.7 per cent to marginal ulcer. The ratio of these three types of ulcers to each other is comparable with that found in any group of ulcers whether bleeding or not. In the intermediate and slight groups a similar ratio of bleeding due to ulcer and other conditions was obtained.

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and response to conservative therapy that might prove of assistance in arriving at a correct diagnosis. The average ages in the ulcer and nonulcer group did not differ significantly, being forty-one and forty-four years respectively. Although the duration of bleeding prior to admission tended to be shorter and other evidences of severity of hemorrhage (fainting, sudden onset, hematemesis) tended to be more pronounced in the patients bleeding from esophageal varices than in the other groups, little statistical difference could be found between the ulcer and nonulcer groups if they were taken as a whole. Hematemesis was absent in a considerable number of each group but not enough in any one to help in distinguishing the various diagnoses in question. It was present in all the patients who died or were operated on and in 65 per cent of the patients with duodenal ulcer and massive hemorrhage. It occurred in only 40 per cent of the less severely bleeding ("intermediate") group. We must agree with Meulengracht⁶ that in general the absence of hematemesis means, even if the ulcer is beyond the pylorus, a less serious degree of bleeding than if it is present.

Although in the ulcer groups some factors that caused emotional or physical strain or overtaxed the gastrointestinal tract were present in over half the patients before they bled from ulcer, the same conditions were observed in almost half the patients bleeding from other causes. The most common of these factors was overindulgence in food or alcoholic beverages or the assumption of unusual responsibility such as is attendant on a business reverse or crisis, an impending marriage or the moving of a household. Infections and the use of salicylates occurred as possible precipitants in both groups. In 60 per cent of the patients with ulcer there was a premonitory symptom of ulcer activity—that is, pain or vomiting. In the nonulcer group false signs of ulcer activity were present in only 4 cases, 2 of which were in the group in which no cause could be found; clinically, these patients were ulcer suspects even though x-ray films failed to show an ulcer crater. This finding is of importance in differential diagnosis and also has obvious prophylactic implications in that it behooves patients with ulcer to heed such symptoms early and to seek treatment promptly.

Sixty-eight per cent of all patients with ulcer who bled suffered ulcer pain during hemorrhage. Among the patients without ulcers there were 3 who had false ulcer pain. Two of these were ulcer suspects but had normal gastrointestinal x-ray films. The other patient also had bleeding of undetermined cause. This symptom, therefore, if present, is a helpful one in making the differential diagnosis between hemorrhage from peptic ulcer and that from other causes. Forty-seven of the 56 patients (84 per cent) with bleeding from peptic ulcer gave a history of previous symptoms of postprandial distress that could be interpreted as being

due to ulcer. False symptoms, sufficient to have suggested a clinical diagnosis of ulcer were present, however, in 11 of the 30 nonulcer bleeders (36.6 per cent), 10 of whom had gastritis or hemorrhage of undetermined cause. This degree of incidence among the nonulcer group suggests that a history of previous symptoms is unreliable in aiding differential diagnosis.

Among the patients with ulcer 35 had had a definite, previous diagnosis of ulcer, confirmed by x-ray study, among the patients without ulcers there were but 2 in whom the diagnosis had been made. A definite previous diagnosis of ulcer, if present, is therefore significant.

The incidence of previous hemorrhage in the patients studied was not significant. No conclusions can be drawn since slightly more than two thirds of our patients were admitted during their first hemorrhage and slightly less than a third during subsequent hemorrhages. Since gastritis is a condition generally associated with multiple hemorrhages, we were surprised to find that only 1 of these patients had bled previously before admission to the hospital.

The drinking habits of the 65 patients of the total of 86 in the series in whom an adequate history in this regard was obtainable are interesting. It is striking that 34, or more than half, of the patients were heavy drinkers, and that this applied to 17 of 21, or 81 per cent, of the nonulcer group, and to 17 of 44, or 38.6 per cent, of the ulcer bleeders. It is of interest that only 1 patient of 21 in the nonulcer group was an abstainer. None of these distinctions, however, were clear-cut enough to help us definitely with differential diagnosis in the individual case.

Physical Examination

The physical examination included inspection for the so-called ulcer facies, a careful search for stigmas of cirrhosis—namely, a large, percussible or palpable liver or spleen and jaundice—and inspection of the face, shoulders, arms and back for spider telangiectasias. It was discovered that during the height of hemorrhage and shock enlarged spleens were often too soft to be felt, and spider telangiectasias too faint to be visible. The degree of arteriosclerosis was always estimated.

Hemoglobin, red-cell counts and hematocrit determinations were made daily as long as signs of hemorrhage persisted and at less frequent intervals thereafter. As soon as possible, determinations were made to rule out the presence of a hepatic or metabolic disturbance.

Emergency X-ray Study

The early roentgenologic examination in patients bleeding from the gastrointestinal tract was initiated by Hampton⁷ and has been discussed by Schatzki,⁸ who gives a thorough description of the technic. Here we shall only mention in brief that a thin

other than ulcer died, however—a mortality of 30 per cent. Table 2 reveals the causes of death in the 11 cases of massive bleeding. Two facts of interest stand out here. The first is that in only 6 of the 11 cases was hemorrhage the primary cause of death. In the other 5 the patients died of other

operation, of lobar pneumonia. Here arteriosclerosis played no part, but portal hypertension, which had developed after a traumatic portal-vein thrombosis, and pneumonia made the bleeding ultimately fatal. The second death from ulcer was in a sixty-seven-year-old man with a gastric ulcer, advanced

TABLE 1 Upper Gastrointestinal Bleeding in Patients with and without Ulcer

DIAGNOSIS	MASSIVE HEMORRHAGE		INTERMEDIATE HEMORRHAGE		SLIGHT HEMORRHAGE		TOTAL CASES	TOTAL DEATHS
	NO. OF CASES	NO. OF DEATHS	NO. OF CASES	NO. OF DEATHS	NO. OF CASES	NO. OF DEATHS		
Patients with peptic ulcer								
Duodenal ulcer	48	0	29	1*	26	0	103	1
Gastric ulcer	7	2	3	0	0	0	10	2
Marginal ulcer	1	0	1	0	2	0	4	0
Totals	56	2	33	1	28	0	117	3
Patients without ulcer								
Esophageal varices	8	7	3	0	2	0	13	7
Gastritis	6	0	6	0	7	0	19	0
Other†	2	2	1	1	0	0	3	3
Cause undetermined	14	0	7	0	8	0	29	0
Totals	30	9	17	1	17	0	64	10
Grand totals	86	11	50	2	45	0	181	13

*The primary cause of death was hypertensive cardiovascular disease.

†These diagnoses were carcinoma of the stomach, cirrhosis without demonstrable varices, and leiomyoma of the stomach.

causes—liver failure in 3, peritonitis and malnutrition in 1, and terminal carcinoma of the stomach in 1. Secondly, 10 of the 11 patients who died had either hepatic cirrhosis or portal hypertension as a primary or secondary diagnosis. In the 3 of these 10 that were not bleeding frankly from esophageal varices the sources of bleeding were gastric ulcers in 2 and undetermined in 1. From these facts it appears that one must agree with the conclusion of Meulengracht⁶ that the dangerous bleeders are those whose bleeding is due to or complicated by factors that interfere with nutrition or the normal state of the gastrointestinal blood vessels. Arteriosclerosis is undoubtedly the most common unfavorable complicating factor that renders the hemorrhage

operation and carcinoma of the liver, death occurring within thirty-six hours of admission to the hospital.

MANAGEMENT

All patients with gastrointestinal hemorrhage were admitted to the Medical Service, but within twenty-four hours of arrival and as soon as the diagnosis of massive hemorrhage had been made the patient was seen by the surgical member of the team, who then followed the case with frequent consultations with the internist.

Diagnosis

Since the accurate diagnosis of the source of the bleeding was an important determination in

TABLE 2 Causes of Death in Patients with Upper Gastrointestinal Hemorrhage

PATIENT	AGE	SOURCE OF HEMORRHAGE	AUTOPSY	DEGREE OF HEMORRHAGE	CHIEF CAUSE OF DEATH	OTHER DIAGNOSES
H. W. L.	26	Gastric ulcer	Yes	Massive	Hemorrhage	Portal hypertension, pneumonia
E. P. M.	67	Gastric ulcer	Yes	Massive	Hemorrhage	Cirrhosis of liver, liver-cell carcinoma
W. G. M.	55	Esophageal varices	Yes	Massive	Cirrhosis of liver	Hemorrhage
T. P. J.	52	Esophageal varices	Yes	Massive	Cirrhosis of liver	Hemorrhage, arteriosclerotic heart disease
A. P.	35	Esophageal varices	Yes	Massive	Hemorrhage	Cirrhosis of liver, rectal varices, with rupture
F. W. P.	59	Esophageal varices	Yes	Massive	Hemorrhage	Portal-vein thrombosis, hemorrhage
P. M.	54	Esophageal varices	Yes	Massive	Hemorrhage	Peritonitis
T. H.	52	Esophageal varices	No	Massive	Hemorrhage	Cirrhosis of liver
J. R. G.	43	Esophageal varices	Yes	Massive	Hemorrhage	Cirrhosis of liver
J. J. G.	57	Carcinoma of stomach	Yes	Massive	Carcinoma of stomach	Cirrhosis of liver
W. A. B.	51	Gastric mucosa	Yes	Massive	Cirrhosis of liver	Hemorrhage

dangerous. We believe, however, that it is not the only one. Others, such as portal hypertension and hepatic cirrhosis, were important in our series. One of the 2 deaths from massive bleeding in peptic ulcer occurred in a twenty-six-year-old man with a gastric ulcer who died, two days after an emergency

any surgical therapy was to be undertaken, special attention was paid to the diagnosis as obtained by the usual methods and to the reliability thereof. In addition, a study was made in the cases of massive hemorrhage of certain special considerations, such as previous diagnoses, habits, type of bleeding

and response to conservative therapy that might prove of assistance in arriving at a correct diagnosis. The average ages in the ulcer and nonulcer group did not differ significantly, being forty-one and forty-four years respectively. Although the duration of bleeding prior to admission tended to be shorter and other evidences of severity of hemorrhage (fainting, sudden onset, hematemesis) tended to be more pronounced in the patients bleeding from esophageal varices than in the other groups, little statistical difference could be found between the ulcer and nonulcer groups if they were taken as a whole. Hematemesis was absent in a considerable number of each group but not enough in any one to help in distinguishing the various diagnoses in question. It was present in all the patients who died or were operated on and in 65 per cent of the patients with duodenal ulcer and massive hemorrhage. It occurred in only 40 per cent of the less severely bleeding ("intermediate") group. We must agree with Meulengracht⁶ that in general the absence of hematemesis means, even if the ulcer is beyond the pylorus, a less serious degree of bleeding than if it is present.

Although in the ulcer groups some factors that caused emotional or physical strain or overtaxed the gastrointestinal tract were present in over half the patients before they bled from ulcer, the same conditions were observed in almost half the patients bleeding from other causes. The most common of these factors was overindulgence in food or alcoholic beverages or the assumption of unusual responsibility such as is attendant on a business reverse or crisis, an impending marriage or the moving of a household. Infections and the use of salicylates occurred as possible precipitants in both groups. In 60 per cent of the patients with ulcer there was a premonitory symptom of ulcer activity—that is, pain or vomiting. In the nonulcer group false signs of ulcer activity were present in only 4 cases, 2 of which were in the group in which no cause could be found; clinically, these patients were ulcer suspects even though x-ray films failed to show an ulcer crater. This finding is of importance in differential diagnosis and also has obvious prophylactic implications in that it behooves patients with ulcer to heed such symptoms early and to seek treatment promptly.

Sixty-eight per cent of all patients with ulcer who bled suffered ulcer pain during hemorrhage. Among the patients without ulcers there were 3 who had false ulcer pain. Two of these were ulcer suspects but had normal gastrointestinal x-ray films. The other patient also had bleeding of undetermined cause. This symptom, therefore, if present, is a helpful one in making the differential diagnosis between hemorrhage from peptic ulcer and that from other causes. Forty-seven of the 56 patients (84 per cent) with bleeding from peptic ulcer gave a history of previous symptoms of postprandial distress which could be interpreted as being

due to ulcer. False symptoms, sufficient to have suggested a clinical diagnosis of ulcer, were present, however, in 11 of the 30 nonulcer bleeders (36.6 per cent), 10 of whom had gastritis or hemorrhage of undetermined cause. This degree of incidence among the nonulcer group suggests that a history of previous symptoms is unreliable in aiding differential diagnosis.

Among the patients with ulcer 35 had had a definite, previous diagnosis of ulcer, confirmed by x-ray study, among the patients without ulcers there were but 2 in whom the diagnosis had been made. A definite previous diagnosis of ulcer, if present, is therefore significant.

The incidence of previous hemorrhage in the patients studied was not significant. No conclusions can be drawn since slightly more than two thirds of our patients were admitted during their first hemorrhage and slightly less than a third during subsequent hemorrhages. Since gastritis is a condition generally associated with multiple hemorrhages, we were surprised to find that only 1 of these patients had bled previously before admission to the hospital.

The drinking habits of the 65 patients of the total of 86 in the series in whom an adequate history in this regard was obtainable are interesting. It is striking that 34, or more than half, of the patients were heavy drinkers, and that this applied to 17 of 21, or 81 per cent, of the nonulcer group, and to 17 of 44, or 38.6 per cent, of the ulcer bleeders. It is of interest that only 1 patient of 21 in the nonulcer group was an abstainer. None of these distinctions, however, were clear-cut enough to help us definitely with differential diagnosis in the individual case.

Physical Examination

The physical examination included inspection for the so-called ulcer facies, a careful search for stigmas of cirrhosis—namely, a large, percussible or palpable liver or spleen and jaundice—and inspection of the face, shoulders, arms and back for spider telangiectasias. It was discovered that during the height of hemorrhage and shock, enlarged spleens were often too soft to be felt, and spider telangiectasias too faint to be visible. The degree of arteriosclerosis was always estimated.

Hemoglobin, red-cell counts and hematocrit determinations were made daily as long as signs of hemorrhage persisted and at less frequent intervals thereafter. As soon as possible, determinations were made to rule out the presence of a hepatic or metabolic disturbance.

Emergency X-ray Study

The early roentgenologic examination in patients bleeding from the gastrointestinal tract was initiated by Hampton⁷ and has been discussed by Schatzki,⁸ who gives a thorough description of the technic. Here we shall only mention in brief that a thin

barium suspension was used, that the patient was examined in the prone and supine positions only, and that compression technic was not employed. Our indications for such emergency x-ray examination were as follows: persistent or recurrent bleeding in a patient on whom we were prepared to perform urgent surgery if the diagnosis of ulcer was definitely established, recurrent bleeding in a patient in whom previous studies had failed to determine the source of the hemorrhage. In each case the surgical member of the team agreed to the need of emergency x-ray examination, an adequate stock of matched blood for transfusions was on hand,

but six hours later on the ward, and was not fatal. Another patient, a man of fifty-six, entered the hospital with a massive hemorrhage and gave a history of having had a duodenal ulcer for years. To corroborate this he gave a history of having had a perforation sutured six months before and demonstrated an abdominal scar to prove it. Since he was in the older age group and did not respond to medical therapy within forty-eight hours, operation was strongly considered and planned. An emergency barium meal was thought by many to be superfluous in this case. It was performed, however, and large esophageal varices were seen,

TABLE 3 *Results of Operation*

PATIENT	AGE yr	DIAGNOSIS	TYPE OF OPERATION	RESULT
<i>Emergency procedure</i> H W L.	26	Gastric ulcer, portal hypertension	One stage gastrectomy	Death 2 days after operation from lobar pneumonia
<i>Urgent procedures</i> C A	55	Duodenal ulcer malnutrition early cirrhosis	One stage gastrectomy without excision of ulcer	Excellent
J I C	60	Duodenal ulcer	One-stage gastrectomy	Excellent
F W C	39	Duodenal ulcer	One-stage gastrectomy	Excellent
T R C	40	Duodenal ulcer extensive penetration with inflammatory mass	Two-stage gastrectomy	Excellent
T H F	49	Duodenal ulcer extensive penetration with inflammatory mass	Two-stage gastrectomy	Excellent
J W F	60	Duodenal ulcer cholelithiasis and cholecystitis	One-stage gastrectomy	Excellent
E J L.	57	Duodenal ulcer extensive penetration following recent perforation	One-stage gastrectomy	Excellent
C O	56	Duodenal ulcer diabetes mellitus	One stage gastrectomy	Excellent
J P M	53	Gastric ulcer extensive pancreatic penetration	One stage gastrectomy, without excision of ulcer	Excellent
J L S *	52	Undetermined cause	Exploration no source of bleeding found	Excellent

*This case is discussed in detail in the text.

and a room was available in the operating suite for the immediate transfer of the patient should further hemorrhage occur or a lesion be found that would indicate that early operation was necessary. All emergency x-ray examinations were rechecked six to twelve days after bleeding had ceased. Of our 86 patients 19, or 22 per cent, had an emergency gastrointestinal series performed during bleeding. In 17 of these patients a satisfactory examination was obtained and a diagnosis made either by positive findings or by exclusion, no additional information being obtained by subsequent elective x-ray study. In 1 patient the examination was unsatisfactory and was recognized as such, so that therapy was not thereby influenced. In another, the first case of the series (J L S, Table 3), a possible diagnosis of duodenal ulcer was made. This was not found at an urgent operation performed on the basis of these x-ray findings. Review of the films taught us that a minimal degree of deformity of the duodenum seen in a gastrointestinal series performed under emergency circumstances cannot be taken as positive evidence of ulcer. In 1 patient only the examination may have contributed to a recurrence of bleeding. This took place not in the X-Ray Department

only a slight deformity being present in the duodenum. Conservative therapy was persisted in and was successful in stopping the hemorrhage, the diagnosis was then further substantiated during a subsequent successful splenorenal anastomosis. In retrospect, if the very positive history of ulcer had been acted upon the patient would have received an unnecessary emergency operation.

Gastroscopy

Gastroscopy was performed as an urgent procedure only during second or repeated admissions of the patients in whom no source for the bleeding had been found by elective examinations during the previous periods of hospitalization. It was helpful in 2 cases, and perhaps should have been utilized more frequently.

TREATMENT

Conservative treatment as initiated on the medical ward did not differ in great extent from that in current practice in the United States. The pulse, blood pressure and blood counts were taken at frequent intervals depending upon the briskness of hemorrhage and the degree of shock. A chart of all stools and vomitus was made. If a history

of hematemesis or other vomiting within twelve hours of admission was obtained the patient was starved rather than fed. Similarly, patients with esophageal varices were not fed until the immediate bleeding and shock had been controlled. Feedings, when initiated, were of small amounts and of the softest types of foods. Careful sedation was carried out by the combined use of small doses of sodium luminal and various narcotics. Early in the series morphine was used rather extensively, but owing to the frequent vomiting that resulted from the use of more than 10 mg (1/6 gr) of this drug a shift to Demerol in 50-mg doses subcutaneously was made and found to be most satisfactory. The early recognition of the cirrhotic patient is most important, since minimal sedation is necessary in this group to avoid the precipitation of hepatic coma. Transfusions were the backbone of the replacement therapy and were given liberally not only to prevent shock but also to restore promptly a sufficient volume of blood so that the red-cell count would be elevated above 3,500,000. The parenteral injections of large doses of vitamins C and K were arbitrarily employed in patients with chronic peptic ulcer who had been on rigid feeding regimes for a long time. Fifty-three and 56 per cent, respectively, of the patients with and without ulcer stopped bleeding within twenty-four hours of admission. Forty per cent of the latter continued to bleed, compared to 21 per cent of the former. In 23 per cent of the patients with ulcer bleeding recurred after having once stopped, and only 1 nonulcer patient experienced a recurrence in bleeding. This is in keeping with our conception of bleeding from peptic ulcer—namely, that the reason for continuation of bleeding is the redigestion of the clot from the bleeding vessel by the strong acid and peptic secretion of the gastric mucosa in the patient with ulcer. A patient who stops bleeding early under medical treatment and then bleeds again may, from this data, be considered more likely to have a peptic ulcer than some other condition as a cause of his bleeding.

Surgical

Surgical operation was carried out in 10, or 18 per cent, of the patients with proved peptic ulcers. From a previous study of the literature (Warren and Lanman⁸) it was apparent that under the best conservative methods available there has always been an irreducible minimum of 1 or 2 patients out of every 20 with massive bleeding from ulcer who do not survive conservative therapy. These patients usually either are elderly or have some specific complicating factor besides the ulcer itself. We have considered it impossible to determine which of the patients in these groups is going to stop bleeding on medical therapy without spending many days in a therapeutic trial, which, if unsuccessful, leaves the patient in a poor state for

operation. We have adopted, as the result of our experience, a policy of operating at an early period on all patients over approximately forty years of age with bleeding from peptic ulcer that does not stop within forty-eight hours of entry or, having once stopped, begins again to an appreciable degree. In addition, operation was seriously considered on the basis of the same temporal indications when the diagnosis of extensive penetration was made or a complicating disease such as cirrhosis or diabetes mellitus was present. Wood⁹ has recently pointed out the high incidence of bleeding in diabetic patients with ulcer. This policy necessitates the inclusion in the operative group of many patients who would have stopped bleeding on a medical regime had it been continued. It is only justifiable, then, if it includes all the patients whose hemorrhage would not have stopped on a medical regime. This we believe to be the case with the exception of the rare patient who exsanguinates within forty-eight hours of admission.

We have believed that, to justify a policy of urgent operation on a selected group of patients, rigid requirements must be insisted upon. The diagnosis must have been confirmed by x-ray study and, to decrease the risk, the operation performed must be simplified in certain patients. For example, in comparison with the conventional gastric resection it may occasionally be considered wiser, in patients in whom the ulcer is very difficult to remove because it lies posteriorly in the gastroduodenal segment, to leave that ulcer in situ (Warren and Lanman⁸). In the latter instance, although it has not occurred in our experience, recurrent hemorrhage from the ulcer that has not been removed has been described (Welch¹⁰). We consider, however, that having performed such a procedure in a patient bleeding from duodenal ulcer and the ulcer having bled again, one is in a stronger position than if such a (first-stage) procedure had not been done. In the first place we have assurance that the ulcer will heal within a few weeks at the longest (McKittrick, Moore and Warren¹¹) and, secondly, if, rarely, further surgery seems advisable to stop hemorrhage, it can be done with the attention focused thoroughly on this objective. It helps the surgeon greatly to know that no gastrojejunal anastomosis need be done after eradication of the ulcer has been performed, and also that the patient can eat enough to maintain nutrition soon after operation. This is essential if liver disease is present.

The group of patients, all "proved" cases of ulcer, in whom the decision to operate was made, are shown in Table 3. The operations were graded as emergency when the patient's hemorrhage continued faster than replacement therapy could restore it, and urgent when bleeding was continuing but at a slow enough rate so that a red-cell count of 3,500,000 or higher could be restored before operation was begun. The 1 death, in a case of gastric ulcer

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BRILL'S DISEASE*

Report of 3 Cases with Aureomycin Treatment in 2

NATHAN BLUMBERG, M D † JOSEPH C DOANE, M D, ‡ AND LAURENCE B WEISS M D §

PHILADELPHIA

CASE REPORTS

BRILL'S disease should be considered as a cause of fever of undetermined origin in a general hospital that draws patients from the foreign-born population

Typhus fever, a scourge of all times and all nations, was first differentiated from measles in Italy by Jerome Cardan in 1536. Bravo, in 1570, and Fracastorius, in 1584, further described the disease, though the cause was not surmised. In 1608 Cober described the "Hungarian disease," which was prevalent in that army, and noted the presence of lice infestation among soldiers but did not relate them etiologically to what apparently was epidemic typhus. Five hundred and three years later, Nicolle discovered that the body louse could transmit this disease from monkey to monkey. He also observed that in a hospital where the patients' clothing was removed on admission no cases of typhus developed, except among the attendants who handled the discarded infested clothing.

Epidemic typhus accompanies war, and during World War I it was prevalent in Serbia, Germany, Austria, Russia and Poland. This type of typhus is caused by *Rickettsia prowazeki*, which utilizes the body louse as the vector. A second variety of the disease, known as endemic typhus, is constantly prevalent in the southeastern United States. This malady is somewhat milder than the former and differs in that the vector is the rat flea.

A mild sporadic variety of typhus was reported in 1898 by Brill¹ in New York. By 1910 this investigator had collected and reported 221 cases.² Zinsser,³ in 1934, reviewed the subject and suggested that patients who had once lived in an area where an epidemic of typhus fever had occurred and in whom clinical symptoms resembling typhus later developed were manifesting an exacerbation of a long-dormant typhus infection.

Three cases all in Russian-born persons admitted to the hospital with fever of undetermined origin, in which subsequent study established the diagnosis of Brill's disease are reported below. The patient in Case 1 was treated conservatively, whereas the latter 2 received aureomycin. The specific organism (*R. prowazeki*) was isolated in Cases 2 and 3.

CASE 1 S P, a 40-year-old housewife, was admitted to the hospital on June 21, 1948, with a chief complaint of fever and headache and discharged on July 13.

The present illness had begun 11 days prior to admission with vague prodromes of fatigability and irritability. The onset of fever occurred 4 days prior to admission. While the patient remained at home, the temperature varied from 101 to 104°F, and this was accompanied by headache and sweating. Her physician treated her with sulfonamides and penicillin without effect, and she was admitted to the ward service.

The past history revealed that in 1921, at the age of 13, the patient had migrated to America from Kiev, Russia. As far as she could recall she had had no serious febrile diseases either in Europe or in this country.

Physical examination showed a well developed and well nourished but dehydrated woman, who did not seem dangerously ill. The pupils reacted to light and accommodation. Slight conjunctival injection was present. The chest was normal except for bronchial breathing over the right lower lobe. There was no lymphadenopathy. Rectal and pelvic examinations were negative.

The temperature was 104.4°F, the pulse 94, and the respirations 26 per minute. The blood pressure was 128/80.

During the first 36 hours the temperature ranged between 101 and 104°F, and nonspecific drugs with cooling sponges comprised the therapy adopted. On the 3rd morning the temperature dropped to 98.6°F, and a macular rash was noticed on both upper extremities and over the sides of the abdomen. This spread during the day to include the arms, forearms, upper part of the chest and back. The rash became maculopapular and discrete. The lesions were reddish, with some brownish discoloration. Twelve hours after it was first observed, the rash faded, leaving only slight pigmentation. The patient again became febrile, the temperature ranging between 102 and 103°F, and continued so until the 6th hospital day when the temperature became normal and remained so until discharge.

On admission the patient was very irritable and complaining. On the morning of the 4th hospital day she became increasingly irritable, dull drowsy and apathetic. She was unresponsive and appeared exhausted. After defervescence, she became clearer mentally and gradually regained her appetite, and it was possible to maintain hydration without intravenous administration of fluids.

Röntgenologic examination of the chest showed the lungs to be clear and well aerated. The right hilar markings were accentuated but there was no evidence of pneumonitis. Electrocardiograms were normal.

Urinalysis and urine culture were normal on admission, but later after pyuria developed, microscopic examination showed many pus cells and a hemolytic *Staphylococcus albus* and *Aerobacter aerogenes* grew on culture.

Examination of the blood showed a red-cell count of 4,480,000, with a hemoglobin of 14.8 gm and a white-cell count of 10,350 with 76 per cent neutrophils, 1 per cent monocytes and 23 per cent lymphocytes. There were 71 per cent filamented and 29 per cent nonfilamented forms. During the course of the illness, the red-cell count dropped to 3,600,000, and the hemoglobin to 12 gm. The total white-cell and differential count remained stationary. The sedimentation rate was 54 mm per hour (Wintrobe method). The blood Wassermann test was negative. The blood sugar, urea nitrogen and total protein were normal.

Blood cultures on admission and on three subsequent occasions failed to reveal any organism. A stool culture showed only colon bacilli.

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with severe portal hypertension, was the emergency case and has been discussed above. Of the 10 patients whose operations were regarded as urgent 4 had extensive penetrations with large inflammatory masses, 2 were complicated by liver or biliary-tract disease, and 1 was a diabetic patient. Two others were aged thirty-nine and sixty years, but had no specific complications of their duodenal ulcers. The tenth patient (J L S, Table 3) has been referred to above. It is impossible to estimate how many of these patients would have survived if conservative treatment had been continued, but from our previous clinical experience we believe that not over half the group would have survived.

DISCUSSION

From these studies our ability to make a differential diagnosis of upper-gastrointestinal-tract hemorrhage at the time of active bleeding on clinical grounds alone is limited. It can be made fairly accurately if one weighs carefully certain positive and negative findings of the history and physical examination. Two unusually helpful and accurate facts in the diagnosis of peptic ulcer in our series were a previous diagnosis of ulcer by a physician and the presence of pain during the bleeding episode.

Our attitude toward emergency x-ray examination is that it is the one indispensable maneuver in the diagnosis of the source of bleeding, but that although it is generally a safe procedure it is not necessary unless the x-ray findings are to change any course of therapy that has already been instituted. This obviously applies to its place in the selection of patients in whom surgical rather than medical therapy will be undertaken.

The majority of patients with hemorrhage of various degrees of severity continue to be successfully treated by conservative methods, the backbone of which is adequate blood replacement. Almost invariably the cases of ulcer in which the patients do poorly are those complicated by some additional disease. This may be vascular, hepatic or metabolic, but its prompt recognition by the internist is essential if he and the surgeon are to make an intelligent decision regarding the method of therapy. Thus, an earlier and more radical

surgical approach to the bleeding ulcer complicated by arteriosclerosis, cirrhosis or portal hypertension, diabetes or penetration resulted in a lower mortality than we believe would have occurred had such a policy not been in effect.

SUMMARY

A combined medical and surgical team directed therapy in 86 cases of massive upper gastrointestinal hemorrhage, 56 of which were due to peptic ulceration. The mortality of the patients with ulcer was 3.6 per cent, and that of the nonulcer bleeders 30 per cent.

Emergency gastrointestinal x-ray films were taken when the course of the bleeding or the presence of certain complications suggested that urgent operation might be performed if the presence of an ulcer as the source of the hemorrhage could be definitely established. Satisfactory x-ray films were obtained in 17 actively bleeding patients, and in only 1 case was the bleeding possibly aggravated by the procedure.

Urgent operation was successfully carried out in 9 cases after the establishment of a definite diagnosis of peptic ulcer. An additional patient was operated on as an emergency, and died two days postoperatively. These patients had been selected because of continued bleeding over forty-eight hours, age or the presence of certain complicating diseases, notably portal hypertension.

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This was the fifth case of suspected Brill's disease studied by the Army Epidemiological Board working at the Laboratories of Harvard School of Public Health in which rickettsial identification justified a positive diagnosis

CASE 3 M T, a 55-year-old contractor, was admitted to the hospital on April 21, 1949, with the chief complaint of chills and fever

On March 27 the patient had been discharged from the Jewish Hospital after a colectomy and ileosigmoidostomy for carcinoma of the colon Three weeks after discharge, during the convalescent period following his operation, he had become ill with the present illness Four days prior to admission, he had noted malaise and increasing weakness On the next day, the temperature was 105°F, and he suffered severe shaking and chills During the next 48 hours, he became increasingly toxic, the temperature remaining between 101 and 105.6°F He complained of severe headache. He was admitted to the Jewish Hospital on the 4th day of fever

Thirty-seven years previously in Galicia, Poland, he had had an epidemic illness of several weeks' duration, with chills and fever It is assumed that this was typhus, which was prevalent in eastern Europe at that time. He emigrated to the United States at the age of 19

Physical examination showed a severely toxic patient whose condition resembled the so-called typhoidal state The temperature was 102.8°F, the pulse 120, and the respirations 26 He was irritable and confused The chest was clear except for transient rales at the right infrascapular area The abdominal wounds in the right lower and left lower quadrant were indurated but showed no evidence of infection Rectal examination was negative except for marked irritation around the anus

Early the next morning, a discrete maculopapular rash was noted on the trunk During the day, this spread to the back and the upper and lower extremities It did not involve the palms or soles The lesions blanched on pressure and were slightly pigmented The patient remained febrile and toxic and complained of headache In view of the history of a febrile illness in his native country and the sustained fever, chills, headache, mental state and rash, the diagnosis of Brill's disease was suggested

On the morning of the 6th day of fever, after appropriate laboratory tests had been made, aureomycin was administered orally That afternoon, the rash began to fade, and 24 hours after the administration of the drug, the skin was clear except for the axillary areas and the dorsa of the feet, within 48 hours, it had virtually disappeared Twenty-four hours after the start of aureomycin, the patient was improved His appetite was better, he was able to take some food, and his mental attitude changed Because of the ileosigmoidostomy, camphorated tincture of opium was given to prevent the too rapid passage of the aureomycin through the bowel Forty-eight hours after the beginning of specific therapy, on the 8th day, the temperature fell to normal and he was markedly improved Improvement continued until discharge from the hospital on the 13th day

Aureomycin was begun in doses of 250 mg every hour for three doses and then every 2 hours until he became afebrile. The drug was continued every 4 hours for 24 hours and then for every 6 hours for 48 hours He received a total of 10 gm of aureomycin orally

On admission the red-cell count was 4,100,000 with 12 gm of hemoglobin, and the white-cell count was 9300, with 46 per cent neutrophils, 4 per cent monocytes and 10 per cent lymphocytes There were 20 filamented and 80 nonfilamented forms Urinalysis, the blood urea nitrogen and a blood culture were negative. Roentgenographic examination of the chest showed the lung fields to be normal There was no evidence of metastasis or other tumor

Capsules containing lice were implanted on this patient on the 6th day, and subsequent animal study was successful in isolating the rickettsias

Agglutination tests for *E. typhosa* O and H, paratyphoid A, paratyphoid B, brucellosis and *P. OX-19* were negative on the 5th and 8th days of fever

Complement-fixation tests with the specific antigens of epidemic and murine typhus were done at the Virus Diag-

nostic Research Laboratory of the Children's Hospital, Philadelphia The results are presented in Table 3

This patient had been convalescing at home after an operation and had no possibility of becoming infected by the vectors of typhus The isolation of the causative rickettsia,

TABLE 3 Complement-Fixation Tests in Case 3

DAY OF TEST	EPIDEMIC-TYPHUS TITER	MURINE-TYPHUS TITER
6th	1 8	1 2
8th	1 128	1 8
13th	1 1024	1 256
20th	1 1024	1 128

together with the complement-fixation tests, indicated the diagnosis of Brill's disease

DISCUSSION

It is to Brill^{1, 2} and Zinsser^{4, 5} that the current concepts of this clinical entity are due It had previously been assumed that this disease was related to the murine or endemic typhus described by Maxcy⁶ as occurring in Mexico and the southeastern United States

Between 1910 and 1933, in New York and Boston, 538 cases of Brill's disease were observed About 95 per cent of these cases occurred in foreign-born persons, 93.6 per cent of whom had been born in the endemic typhus regions of Europe, with 80 per cent from Russia alone About 90 per cent of the patients were Jewish This preponderance is easily understood if one realizes that in that period immigration to this country consisted largely of the Jewish populations of the regions It was also clear that patients in the second decade studied were about ten years older than those in the earlier group None of the cases could be traced to the usual vectors, and it was shown that almost every patient was from a different home

From bacteriologic studies, Zinsser ascertained that the virus of Brill's disease behaved like the European type He concluded that a certain percentage of patients who have had typhus at an early age remain clinically well for years, but during this time are carriers of the disease and may later suffer a second attack This variety of typhus is now named Brill's disease.

Blatteis⁷ reported a series of 138 cases of this disease and confirmed Brill's observations Ninety-five per cent of his patients were Jewish immigrants from Russia None of the cases could be traced to exposure, and none of the hospital personnel contracted the disease, although no special precautions were taken Lewis,⁸ at the Pennsylvania Hospital, reported 13 cases with similar observations

Morgan et al.⁹ recently described 2 cases of Brill's disease occurring in Irish-born immigrants who had lived in Boston for over thirty years The possibility of recent infection was ruled out so that the

The spinal fluid obtained at the height of the mental torpor was clear with a count of 9 lymphocytes per cubic millimeter. Culture failed to reveal any pathogens.

Attempts were made, beginning on the 9th day of fever, to isolate the causative rickettsia. Several samples of whole blood, the buffy coat of spun-down citrated blood and a bone-marrow specimen obtained from the sternal marrow were injected into animals. Three colonies of lice enclosed in special capsules were allowed to feed on the patient for varying periods, and animal inoculations were then done.

Isolation attempts by all these methods were unsuccessful. No rickettsia could be demonstrated.

Agglutination tests for *Eberthella typhosus* (strains O and H), paratyphoid A, paratyphoid B, brucellosis and *Proteus OX-19* were negative on admission and again 2 days later. On the 14th day of fever the agglutination for *P. OX-19* became positive in a titer of 1:320. On the 23rd day the titer increased to 1:640.

At the Virus Diagnostic Research Laboratory of the Children's Hospital of Philadelphia, complement-fixation tests were performed with the following results: the titers for epidemic typhus and murine typhus were, respectively, 1:64 and 1:16 on the 7th day and 1:2048 and 1:512 on the 15th day.

Confirmation was obtained by serologic studies made by the Army Epidemiological Board working at the Laboratories of Harvard School of Public Health under the direction of Dr. Edward S. Murray, who reported the results shown in Table 1. Thus there was serologic evidence of infection with the rickettsia of epidemic typhus.

She gradually regained her strength and well being and had no sequelae, with the exception of a mild pyuria begin-

TABLE 1 Complement-Fixation Tests for Epidemic and Murine Typhus in Case 1

DAY OF TEST	EPIDEMIC-TYPHUS TITER	MURINE TYPHUS TITER
7th	1:80	1:20
9th	1:640	1:80
14th	1:640	1:160
17th	1:1280	1:160
22nd	1:320	1:80
49th	1:320	1:80

ning on the 15th day, undoubtedly subsequent to the repeated catheterizations.

She was seen for a follow-up examination 2 months after discharge and was clinically well.

Since the patient had had no recent exposure to the known vector of epidemic typhus this was assumed to be a case of Brill's disease.

CASE 2. A F, a 41-year-old locksmith, was admitted to the Medical Service on January 22, 1949.

This patient had been well until 5 days before admission, when he complained of a toothache. On the following day he developed a headache, which persisted, together with malaise, nausea, vomiting and fever. Associated with these symptoms were abdominal distention and pain. On the next day, the temperature varied between 103° and 105°F. Three hundred thousand units of penicillin was administered daily for 4 days along with a sulfonamide. When seen at home by one of us just prior to admission, he presented a picture of febrile toxicity, the cheeks were flushed, the eyes dull, and the appearance then was strongly suggestive of typhoid fever. A fine reddish macular rash, which blanched on pressure, was observed on the trunk. Mouth hygiene was poor, and the gums bled easily on pressure. There was evidence of a pneumonitis at the right base. The abdomen was moderately distended, but no masses were felt.

Later that day, the patient was admitted to the hospital, and a more careful history and physical examination were possible. He complained of pains over the frontal area, beneath the sternum and generally over the abdomen. He was quite dehydrated, and the rash on the abdomen seemed more diffuse than it had been a few hours earlier. The edge of the liver was just palpable beneath the costal margin. A provisional diagnosis of septicemia arising from an infected tooth, virus pneumonitis or a rickettsial disease was made.

It was further learned that the patient had been born in Kiev, Russia, and that at the age of 6 he had contracted either typhus or typhoid fever, probably the former. He had been entirely well until the present illness. He had come to the United States at the age of 16. His locksmith shop was located adjacent to a pet shop, where mice and rats were sold. With this history, the attention of the examining physician turned to the possibility that the patient was suffering with recrudescence epidemic typhus fever (Brill's disease).

On the next day, the toxicity persisted, the temperature remaining high (103°F) and the pulse 100 per minute. On the 3rd day after admission, the rash seemed to fade on the abdomen but was still present on the arms and the legs. Lice colonies were implanted on the patient by Dr. Edward S. Murray, of the Army Epidemiological Board, working at the Laboratories of Harvard School of Public Health. Aureomycin was then begun on the 8th day of illness. One thousand milligrams was given for the first dose, followed by 750 mg every 6th hour for 2 days, 500 mg every 6th hour for 3 days and 250 mg at like intervals for the next 2 days. In all, 13 gm of aureomycin was administered over an 8-day period. The temperature fell to 100°F 14 hours after the beginning of aureomycin therapy, but in the next 10 hours it rose to 104°F, remaining so for 8 hours, and then rapidly declined to normal on the 10th day of the disease. The patient continued to improve rapidly, was allowed out of bed on the 14th day and was discharged on February 6.

On the day after admission the red-cell count was 4,470,000, with 11.8 gm of hemoglobin, and the white-cell count was 12,350, with 73 per cent neutrophils, 23 per cent lymphocytes and 4 per cent monocytes. A count of filamented and nonfilamented forms showed a marked shift to the left. The blood urea, chloride and sugar were within normal limits. Blood cultures repeated on three occasions were negative. Roentgenologic examination of the chest at the time of admission showed increased bronchovascular markings. A plain film of the abdomen was normal. An electrocardiogram showed a sinus tachycardia. Smears from the gums were positive for Vincent's organisms. A stool was negative for ova and parasites.

Capsules containing lice were implanted on this patient on the 7th day of illness for 13½ hours. Subsequently, these lice were placed on a normal rabbit for 11 days. At the end of this time, 120 lice remained alive. These were ground up and injected intraperitoneally into x-ray cotton rats. Five days later the rats were very sick, were killed and

TABLE 2 Complement-Fixation Tests in Case 2

DAY OF TEST	EPIDEMIC TYPHUS TITER	MURINE TYPHUS TITER
7th	1:512	1:128
10th	1:2048	1:1024
16th	1:2048	1:1024

smears from their peritoneal exudate showed large numbers of intracellular and extracellular organisms, which when stained by the Macchiavelli method were recognized as typical rickettsias. These rickettsias are now being further studied with immunity and other animal methods to differentiate them from murine-typhus strains. It seems from the clinical picture of this patient and from his history, that these rickettsias will be identified as the specific etiologic strain causing recrudescence epidemic typhus.

On admission the agglutination tests for *E. typhosa* O and H, paratyphoid A, and paratyphoid B, *Brucella abortus* and *P. OX-19* were negative. On the 10th day of illness, the agglutination for *P. OX-19* was ++++ and ++++, respectively, in dilutions of 1:20 and 1:40. On the 12th day of illness, the agglutinations for *P. OX-K* and *OX-2* were negative from a titer of 1:20 through 1:1280. On the 15th day of illness, tests for *P. OX-19* were positive in 1:320 dilution. On the 20th day of illness tests for *P. OX-19* were positive in dilutions of 1:20 to 1:80 but negative in dilutions of 1:160 to 1:320.

Serum was sent to the Virus Diagnostic Research Laboratory of the Children's Hospital, where complement-fixation tests were performed and the results shown in Table 2 were obtained.

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ARTANE IN THE TREATMENT OF PARKINSON'S DISEASE

A Report of Its Effectiveness Alone and in Combination with Benadryl and Parpanit

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BOSTON

THIS report is a clinical evaluation of a recently synthesized drug called Artane† in 44 cases of Parkinson's disease. Artane is a piperidyl with the formula shown in Figure 1, on which also are written the structural formulas of Benadryl and Parpanit for comparison. These three chemicals are not similar in structure to either atropine or scopolamine.

The details of the chemical behavior and the pharmacologic and physiologic effects of the drug in animals are available in the reports of the manu-

the therapy of Parkinson's disease with the newer drugs.

By means of such a chart it is possible gradually to reduce the medication that the patient is taking when first seen and, at the same time, slowly to increase the dose of Artane. Sudden withdrawal of the antispasmodic effects of the atropine drugs is avoided by this means. A further advantage of such gradual overlapping of medication is the knowledge of the value in a particular patient of the two drugs together.

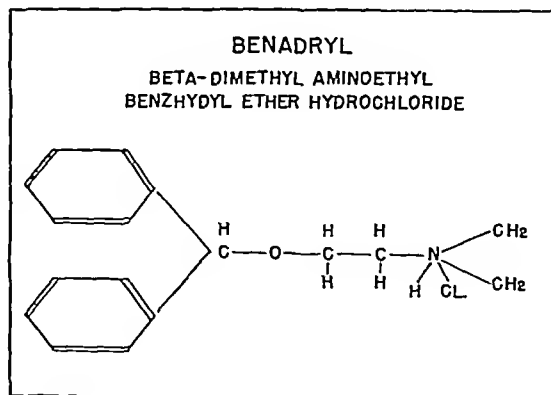
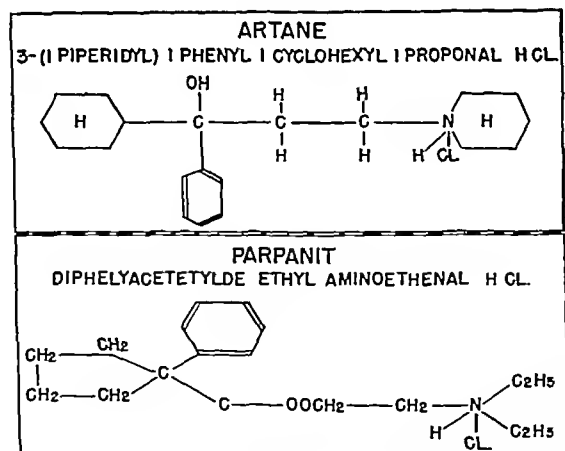


FIGURE 1 Comparative Structural Formulas of Artane, Benadryl and Parpanit

facturer and will be published shortly. It is safe to use, has no serious side effects, is promptly eliminated and has no disturbing effects on the blood or the renal or cardiac system.

The hourly schedule chart devised by Viets and Schwab¹ and in use in the treatment of patients with myasthenia gravis is extremely valuable in

An example of the regulation by slow reduction of the belladonna drug and increase in Artane is shown in Figure 2 and in the following case:

A 44-year-old woman with a history of severe influenza in 1919 and the onset of slowness in motion of the left arm 5 years before reporting for treatment had had involvement of the left leg and stiffness, fatigue and loss of fine movements in the fingers for 4 years. The tremor, first in the fingers and later in the wrist, had been present for 3½ years. For 1 year slight involvement in the right arm had been observed. The diagnosis of Parkinson's disease had been made at the onset by her family physician, and scopolamine, stramonium and amphetamine sulfate had been given in the usual doses.

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*Supplies of Artane used in this investigation were furnished by the Lederle Company Pearl River New York.

disease probably represented the recrudescence of a previous infection

During the recent war, new epidemics of typhus swept Europe and Asia. Troops operating in these areas were protected better than ever before by means of new insecticides, careful immunization and rigid quarantine of existing cases. In fact, during the recent war, Gordon¹⁰ reports that only 3 confirmed cases of typhus occurred in the American troops in the European Theater of Operations. All experienced mild attacks. Two returned prisoners of war also were found to have typhus. Scoville¹¹ states that in the Japanese-Korean areas only 28 cases occurred in the occupation forces while an epidemic was raging in those countries. All patients had been vaccinated, and the disease was mild. No deaths resulted. It is surmised that some of the victims of these new epidemics may continue to harbor the organism, resulting in an increased incidence of Brill's disease years hence.

Aureomycin, an antibiotic derived from *Streptomyces aureofaciens*, holds promise of value in this and similar diseases. At the panel meeting of the New York Academy of Sciences held on July 21, 1948, the use of this drug was reported in rickettsial diseases of many types.

Wong and Cox¹² discussed the use of aureomycin in guinea-pig inoculations with *R. prowazeki*. When the drug was started before the febrile reaction to the inoculations had occurred, the fever was aborted. If the medication was begun after the onset of fever, the case was controlled in twenty-four to forty-eight hours, whereas the control animals had fever for approximately seven days.

Anigstein, Whitney and Beninson¹³ confirmed this with similar studies using guinea pigs. Both oral and parenteral administrations of the drug were effective.

Schoenbach, Bryer and Long^{14, 15} reported a case of Brill's disease in which therapy was started on the sixth day. Within forty-eight hours, the patient had become afebrile and asymptomatic.

In the study of a case of fever of undetermined origin, Brill's disease should be considered.

Fever, malaise, intense headache, chills, a skin rash and mental signs occurring in a foreign-born person years after his arrival from an area where epidemic typhus was present should cause one to consider this diagnosis. As previously noted by Schoenbach et al.¹⁵ and again emphasized here, the Weil-Felix reaction cannot be used to exclude this disease. Agglutinations with the specific antigens of epidemic and murine typhus are necessary.

Confirmation of the diagnosis is made by serologic study and growth of the rickettsias on blood culture. Plotz¹⁶ recently studied 23 cases of Brill's disease by means of complement-fixation tests. He found that the serums of the patients gave higher titers with the antigen of classic epidemic typhus than with that of murine typhus, thus lending addi-

tional support to Zinsser's hypothesis. Biopsy of skin lesions may also demonstrate the rickettsias.

Probably one of the reasons for failure to isolate the organism in Case 1 was that lice studies and the withdrawal of blood specimens were not started before the ninth day of the disease, and Murray¹⁷ has found that the ninth day is too late in the course of Brill's disease to obtain the strain.

These 3 cases demonstrate clearly the value of aureomycin in Brill's disease. In Case 1, in which the patient was treated conservatively, spontaneous remission occurred on the eleventh day. In Case 2 aureomycin was begun on the eighth day, and remission occurred on the tenth day. In Case 3 the drug was started on the sixth day, and remission occurred on the eighth day. Early diagnosis with prompt administration of aureomycin leads to a dramatic remission within forty-eight hours.

SUMMARY

Three cases of Brill's disease occurring in persons born in Russia, 2 of whom had a history of epidemic typhus years previously, are presented.

The patients were admitted with a diagnosis of fever of undetermined origin, and all the usual studies were negative.

The final diagnosis of Brill's disease was made by a careful history, serologic study and isolation of the organism.

Oral administration of aureomycin was used in the treatment of two cases with prompt clinical improvement.

We are indebted to Dr. Edward S. Murray, of the Army Epidemiological Board, working at the Laboratories of Harvard School of Public Health, who gave his time, efforts and advice in the special studies. Acknowledgment also is made to Dr. M. Michael Sigel, of the Virus Diagnostic Research Laboratory of the Children's Hospital of Philadelphia, who performed the complement-fixation tests in all 3 cases.

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evaluation (ten points were used in the evaluation of these cases), large numbers of cases, placebo substitution, a long period of treatment, observation by different physicians (three different observers were involved in this investigation), different groups of patients (three separate groups were reported), adequate time on single drugs, a shift in drugs and multiple drugs and specific psychotherapy.

A truly efficient drug should be effective in any hands and not be subject to the individual aptitudes of the investigator. No such remedy is known today, and unless each patient is individually adjusted and frequently and carefully followed, with necessary alterations in dosage schedules, no better results will be obtained with these new compounds than with hvoscine alone.

The effectiveness of Benadryl as a remedy for the symptoms of Parkinson's disease has been confirmed, but the drug is less effective alone than either Parpanit or Artane (2 out of 9 cases). Benadryl in combination with Artane or Parpanit or

even atropine drugs was effective in 12 of 24 cases in which it was tried.

The effect of other antihistaminic drugs, such as Thephorin, aminophylline and Benadryl mixture (Dramamine) is in the process of evaluation.

SUMMARY

The effect of Artane alone and in combination with other drugs in alleviation of the symptoms of Parkinson's disease is reported in 44 cases. Favorable results were obtained in 67 per cent of cases in which treatment with Artane was given.

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ABDOMINAL PAIN IN HEMOCHROMATOSIS*

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BOSTON

AMONG the various manifestations of hemochromatosis are sometimes found certain symptomatic and objective features that simulate acute abdominal conditions. Writers in the medical literature in the United States have given scant notice to the finding of abdominal pain in this disease. Boland and Curran¹ presented one of the few reports of such abdominal symptomatology in hemochromatosis occurring in two brothers. The first entered the hospital with signs and symptoms suggesting cholecystitis. Cholecystectomy was performed, and on pathological examination the gall bladder was found to be normal. However, observation of a brown, cirrhotic liver at operation led to skin biopsy, and the diagnosis of hemochromatosis was made. The patient died on the ninth hospital day in hepatic coma. Later, his brother entered the hospital with similar symptoms. In view of the previous family history, laparotomy was not performed, and skin biopsy again revealed hemochromatosis. The patient recovered with the aid of symptomatic and supportive measures. Hurxthal² reported a case of hemochromatosis, proved by biopsy, that showed marked impairment of renal and adrenal function. Without comment he noted that about one week before admission the patient had had abdominal cramps and diarrhea.

In contrast to the infrequency with which such findings have been reported by American authors is the statistical analysis of the French author Boulin,³ who noted that in 70 cases 34 per cent of patients were originally admitted to the hospital because of painful abdominal crises, those located in the gall-bladder region being especially severe. He pointed out that these patients may even present pseudo-obstructive crises. Furthermore, he stated that spasm of the colon may at times be demonstrated by x-ray examination. In his general review Sheldon⁴ cited an incidence of 6 per cent of patients who showed abdominal pain, 1 per cent having the symptoms with the onset of pigmentation.

Abdominal pain in itself is not an unusual feature of other types of liver cirrhosis, particularly during failure.^{5,6} This pain is not usually associated with tenderness, however. Furthermore, its prognostic implications do not appear to be as immediately ominous as those in the cases presented below, in which the patients died soon after the onset of the abdominal symptoms.

Interest in this subject was stimulated on performance of the autopsy in Case 1. This patient entered the hospital with an abdominal picture that baffled both the medical and surgical services on which he was studied.

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For the past year she had been given Rabellon, 2 tablets four times a day. These belladonna drugs gave her some relief, but produced so much dryness of the mouth, blurred vision and depression of energy that she was thoroughly discouraged.

On the 3rd day of treatment with Artane the patient was relieved of her previously disturbing side effects, and noted a clear-cut increase in motor function, and the loss of fatigue. Rigidity was reduced, and there was a definite elevation of her mood and outlook. On the 7th day the $1\frac{1}{2}$ tablets of Artane (3 mg) produced a mild giddiness with blurred vision that was transient so that she went back to the 2-mg dose every 3 hours according to the instructions given at her first visit.

When seen 2 weeks later she showed objectively less rigidity and tremor—more rapid movements in her fingers, better posture and was subjectively 50 per cent improved (toward her pre-illness status). Objectively by the various tests used she was 25 per cent better than on the belladonna drugs.

A month later, her improvement maintained, she was given Benadryl 50 mg four times a day in addition to Artane, and when seen 6 weeks later she was 5 to 10 per cent better both objectively and subjectively than on Artane alone.

Artane is effective in different dosages in different patients. Overdosage produces side effects similar to those of Parpanit, such as giddiness,

DISCUSSION

In spite of the promising results of the newer belladonna preparations introduced from 1938 to 1942 such as Bulgarian belladonna root, Rabellon, Vinobel, Neoscopolamine and various mixtures, the treatment of Parkinson's disease has not been entirely satisfactory to the patient or the physician. The unpleasant and disturbing side effects, such as dryness of the mouth and blurred vision, occurred with all these compounds. In June, 1948, Budnitz² reported very favorable results with the antihistamine Benadryl, confirmed by Ryan and Wood.³ In March, 1949, Schwab and Leigh⁴ described success with a new synthetic drug, Parpanit. Neither of these substances produced the degree of drying of secretion or interference with accommodation encountered with atropine drugs.

The effectiveness of a treatment against the symptoms of a disease usually varies inversely with

MASSACHUSETTS GENERAL HOSPITAL																					
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MEDICINE		a m	7	8	9	10	11	12	P m	2	3	4	5	6	7	8	9	10	11	12	12 m to 7 a.m.
		6							1												
Rabellon				2				2				2				2					Monday
Rabellon				2				1				2				1					Tuesday
Artane				1½				1½				1½				1½					Tuesday
Rabellon				1				1				1				1					Wednesday
Artane				1½				1				1½				1					Wednesday
Rabellon				1				1				1				1					Thursday
Artane				1				1				1				1					Thursday
Artane				1				1				1				1					Friday
Artane			1			1		1				1			1						Saturday
Artane			1			*1½		1				*1½			1						Sunday
Artane			1			1		1				1			1						Monday
Artane			1			1		1				1			1						2 wk. later
50 mg Benadryl			1			1		1				1			1		1				2 wk later

* = Overdosage

FIGURE 2 Typical Regulation by Slow Reduction of Parpanit and Gradual Increase of Artane

dryness of the mouth, blurring of vision and headache. The initial dose is half a tablet, or 1 mg, four times a day. This is gradually increased until the patient is taking 3 mg five times a day as a high level. The average is 2 mg five times a day.

Artane has been found less toxic than Parpanit in older patients, but it is less effective in reducing tremor. Indeed, in some patients, the tremor is worse in spite of the reduction in rigidity. Of 44 patients who had received Artane for over three months, only 7 (16 per cent) were relieved sufficiently, as compared to their status on atropine, to remain on Artane alone. Nine required the addition of Parpanit, and 7 were best regulated on a combination of Artane and Benadryl. Six others fared best on atropine drugs and Artane.

Twenty-nine, or 67 per cent, were 20 to 30 per cent better after such regulation on Artane than on the medication previously given. Seven were no better, and 8 could not tolerate Artane alone or in combination. Artane was therefore a failure in 33 per cent.

the number of remedies in use. In diabetes, for example, the 90 to 100 per cent success achieved by insulin has led to its replacing other forms of treatment. In Parkinson's disease, in which only 20 to 30 per cent relief of symptoms is possible, over a dozen different medications as well as surgical operation, are available. These newer chemicals do not, unfortunately, alter this deficit, and Artane is not in any sense an "insulin" for these chronic sufferers.

Since the relief of symptoms is only partial in Parkinson's disease, it is not an easy matter to draw accurate comparative results with the newer drugs and the older atropine mixtures. The course of the disease may be affected by spontaneous variation, rest in hospital, special attention, the influence of the observer on the patient, sedative effects, learning curves, enthusiasm of the observer, influence of new tests or drugs, favorable medical changes and effects of concomitant treatment. Greater accuracy may be obtained by objective as well as subjective reports, multiple points in

hemochromatosis whose signs of heart failure disappeared with cortin therapy. Indeed, in the early phases hemochromatosis is most often confused with Addison's disease.^{3, 15} The appearance of diabetes mellitus is a major aid in pointing to the true disease, for primary adrenal insufficiency is extremely rarely associated with diabetes.¹⁶

Since the death of these patients in congestive failure caused by extensive deposition of hemosiderin in the myocardium is now a recognized entity,^{17, 18} pain due to passive congestion in abdominal viscera is a possibility. Hemosiderin deposition may also result in abnormalities in cardiac rhythm,¹⁹ making the patients candidates for embolic phenomena.

Liver failure per se may be the cause of severe abdominal pain.²⁰ However, this is one of the unusual manifestations of this rare disease.

Pancreatitis must also be considered in the differential diagnosis of abdominal pain. In the cases reported above, however, there was no pathological evidence that the pancreas was the cause of the symptoms.

Other painful manifestations of hemochromatosis, such as pain in the extremities,²¹ precordial episodes simulating myocardial infarction but without morphologic findings at post-mortem examination¹⁸ and spasm of the large bowel,² suggest a common etiology in isolated episodes of vasospasm or colic, owing to the immediate effects of hemofuscin deposition in smooth-muscle cells of arteries and of the alimentary tract.²²

Finally, pain in the abdomen in this disease may be a manifestation of abnormalities in glucose metabolism. In hypoglycemia, abdominal pain is possibly due to parasympathetic activity manifested by increased contraction of various segments of the gastrointestinal or biliary tract.²³ Ketosis, which may also be accompanied by acute abdominal pain, tenderness, nausea and vomiting, may be an especially dangerous pitfall because of the often associated abdominal muscular rigidity, leukocytosis and fever.²⁴ In diabetes as difficult to control as that of hemochromatosis, hypoglycemia and ketosis are perennial threats.^{24, 25}

SUMMARY

Attention is called to a clinical syndrome of abdominal pain in hemochromatosis that has been

mentioned very rarely in the medical literature in the United States.

Three autopsied cases showing no morphologic basis for the abdominal episodes are reported. Several possible explanations of this syndrome are presented.

I am indebted to Dr. Frederic Parker, Jr., for his assistance and valuable suggestions.

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Examination of the Boston City Hospital records revealed that in the period between 1936 and 1946 there were 40 cases of hemochromatosis proved by autopsy at this hospital. Of these, abdominal pain was a prominent feature of the clinical course in 6. Three had demonstrable causes for the symptom, 1 had liver failure, 1 had a hepatoma, and 1 had a ruptured diverticulum with peritonitis. The remaining 3 had no morphologic background as a basis for the bizarre abdominal symptomatology. These cases are presented below.

CASE REPORTS

CASE 1 F L, a 41-year-old man, had the diagnosis of diabetes mellitus made in October, 1945. Diet and insulin controlled the diabetes. A few weeks later he experienced upper abdominal pain, nausea and vomiting for 3 days. Several months later there was a recurrence of this pain, described as dull, continuous and nonradiating. On the evening of entry, there was an increase in the severity of the epigastric pain, without radiation. There was some nausea but no vomiting.

Physical examination revealed a well developed, middle-aged man in evident distress. The liver edge was half way between the costal margin and the umbilicus. The entire epigastrium was tender.

The blood pressure was 100/90. The temperature was 98°F, the pulse 114, and the respirations 20.

Laboratory work showed a yellow sugar reduction in the urine. The white-cell count was 14,400. The blood sugar was 265 mg per 100 cc. The carbon dioxide combining power was 45 vol per cent.

Treatment with parenteral injection of saline solution was inaugurated within the first 10 hours. The blood sugar values rose to 450 mg per 100 cc, and during this period a total of 100 units of regular insulin was given. Ten hours after admission there was a green sugar reduction in the urine, but a + acetone test was noted for the first time. The blood chloride on the day after entry was 105 milliequiv per liter (after 2300 cc of saline solution had been given intravenously). The blood sugar fell to 130 mg per 100 cc, and the carbon dioxide combining power to 38 vol per cent. From the time of admission, a shock-like picture developed progressively in spite of plasma and saline administration. About 28 hours after entry the patient was treated for possible adrenal failure. Thirty cubic centimeters of adrenal cortical extract (Upjohn's aqueous extract) and 1500 cc of 1.5 per cent saline solution were given. The patient rallied, and the blood pressure returned to audible limits at 80/60. No further cortical extract was obtainable, and he died 36 hours after admission.

Autopsy (46-57) revealed extensive hemochromatosis involving the liver, pancreas, heart, lungs, kidneys, spleen, bone marrow, lymph nodes, pituitary body and thyroid and adrenal glands. There was no morphologic explanation for the abdominal pain or sudden death.

CASE 2 J F, a 47-year-old man, entered the hospital in June, 1937, with pneumonia. Hepatomegaly and urinary findings indicative of diabetes mellitus were noted. The pneumonia cleared rapidly, and an insulin regimen was instituted. He left against advice 6 days after admission. In January, 1938, he returned for regulation of the insulin dosage. This was found to be quite difficult. Skin biopsy confirmed the suspicion of hemochromatosis. In May, 1938, the patient returned again with midabdominal, cramping pain of 4 days' duration.

Physical examination revealed a well developed, poorly nourished man in no acute distress. The liver extended one handbreadth below the costal margin. There was diffuse abdominal tenderness.

The blood pressure was 130/85, the temperature 98°F, the pulse 80, and the respirations 20.

Laboratory studies showed a green sugar reduction in the urine in addition to a trace of albumin and a + test for bile. The red-cell count was 3,750,000 and the white-cell count was 7200. Blood chemical studies revealed a fasting blood sugar of 267 mg per 100 cc.

The patient showed signs of progressive cardiac decompensation and transitory episodes of fibrillation. On digitalis, ammonium chloride and fluid restriction he made rapid improvement and left against advice 2½ weeks after admission. Within 2 weeks he was readmitted with evidence of dehydration and diabetic coma. He died within 36 hours in spite of vigorous supportive measures.

Autopsy (38-316) showed marked hepatomegaly and evidence of hemochromatosis in the liver, kidney, pancreas and heart.

CASE 3 W T, a 58-year-old man, entered the hospital in April, 1933, with signs and symptoms of scurvy, for which he was treated successfully. In September, 1939, he returned with signs of congestive failure. Four months before his final admission, he returned again with cardiac decompensation, when a diagnosis of arteriosclerotic heart disease with auricular fibrillation was made. The last admission, on February 23, 1945, was again because of cardiac decompensation.

Physical examination showed a middle-aged man in acute distress with orthopnea and dyspnea. There were crackling rales and dullness at the lung bases. The liver edge was palpated four fingerbreadths below the costal margin. Pitting edema of the legs was evident. Slight scleral icterus was noted.

The blood pressure was 112/76. The temperature was 98°F, the pulse 120, and the respirations 26.

Examination of the urine revealed a ++ to +++ test for albumin and a + to ++ test for bile, and the sediment contained occasional red and white cells. The non protein nitrogen was 44 mg, and the fasting blood sugar 115 mg per 100 cc. Studies of liver function demonstrated impairment.

The patient was treated with digitalis, a salt-free diet and ammonium chloride. On this regimen he became asymptomatic and was allowed out of bed on the 4th day. On the 12th hospital day he suddenly complained of abdominal pain and went into a state of peripheral vascular collapse. Twelve hours later he had a similar attack of pain and died. The clinical impression was pulmonary infarction.

Autopsy (45-127), performed 5 hours post mortem, showed arteriosclerotic heart disease, rheumatic heart disease with involvement of the aortic valve, and hemochromatosis involving the heart, lungs, liver, spleen, pancreas, kidneys, gastrointestinal tract, lymph nodes, thyroid, adrenal and parathyroid glands, testes, bone marrow, skin and pituitary body. There was no demonstrable morphologic cause for the pain or sudden death.

DISCUSSION

Many hypotheses can be offered as reasons for these symptoms. One of the most attractive possibilities to account for the episodes of abdominal pain in hemochromatosis is adrenal cortical insufficiency. This symptom, according to Soffer,⁷ occurs in a relatively small percentage of patients with Addison's disease in the intercritical period, but crises are often heralded by gastrointestinal manifestations, including abdominal pain. Adrenal involvement as one of the multiple endocrinopathies of hemochromatosis seems well established.^{2,4,8} Hurxthal's² case is an example. The patient of Layan,⁹ a twenty-nine-year-old man whose pigmentation cleared on massive doses of vitamin C, is possibly another. A relation has been shown between adrenal cortical extracts and vitamin C,¹⁰ and between vitamin C and secretion of adrenal cortical hormones under stress.^{11,12} Moreover, the first case reported above suggested a therapeutically diagnostic response to the adrenal cortical extract administered. Evidence of the same nature is afforded by the report of Oumansky and Longuet¹⁴ in an eighteen-year-old girl with

hemochromatosis whose signs of heart failure disappeared with cortin therapy. Indeed, in the early phases hemochromatosis is most often confused with Addison's disease.^{3, 15} The appearance of diabetes mellitus is a major aid in pointing to the true disease, for primary adrenal insufficiency is extremely rarely associated with diabetes.¹⁶

Since the death of these patients in congestive failure caused by extensive deposition of hemosiderin in the myocardium is now a recognized entity,^{17, 18} pain due to passive congestion in abdominal viscera is a possibility. Hemosiderin deposition may also result in abnormalities in cardiac rhythm,¹⁹ making the patients candidates for embolic phenomena.

Liver failure per se may be the cause of severe abdominal pain.²⁰ However, this is one of the unusual manifestations of this rare disease.

Pancreatitis must also be considered in the differential diagnosis of abdominal pain. In the cases reported above, however, there was no pathological evidence that the pancreas was the cause of the symptoms.

Other painful manifestations of hemochromatosis, such as pain in the extremities,²¹ precordial episodes simulating myocardial infarction but without morphologic findings at post-mortem examination¹⁵ and spasm of the large bowel,² suggest a common etiology in isolated episodes of vasospasm or colic, owing to the immediate effects of hemofuscin deposition in smooth-muscle cells of arteries and of the alimentary tract.²²

Finally, pain in the abdomen in this disease may be a manifestation of abnormalities in glucose metabolism. In hypoglycemia, abdominal pain is possibly due to parasympathetic activity manifested by increased contraction of various segments of the gastrointestinal or biliary tract.²³ Ketosis, which may also be accompanied by acute abdominal pain, tenderness, nausea and vomiting, may be an especially dangerous pitfall because of the often associated abdominal muscular rigidity, leukocytosis and fever.²⁴ In diabetes as difficult to control as that of hemochromatosis, hypoglycemia and ketosis are perennial threats.^{24, 25}

SUMMARY

Attention is called to a clinical syndrome of abdominal pain in hemochromatosis that has been

mentioned very rarely in the medical literature in the United States.

Three autopsied cases showing no morphologic basis for the abdominal episodes are reported.

Several possible explanations of this syndrome are presented.

I am indebted to Dr Frederic Parker, Jr, for his assistance and valuable suggestions.

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MEDICAL PROGRESS

LABORATORY DATA IN CLINICAL MEDICINE UNITS OF MEASURE, COSTS, AND QUANTITATIVE SIGNIFICANCE OF RESULTS*

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THE potential number and cost of laboratory examinations in clinical medicine are enormous. Accordingly, it is a considerable responsibility for the physician to choose wisely the laboratory procedures that are to be performed. Certain

systems of the body for detecting the presence of disease. These procedures include the determination of the hematocrit (or hemoglobin), white-cell count and differential white-cell count, analysis of urine, inspection of the stool, examination for

TABLE 1 Selected Units of Measure from the Metric System, and Relations among Them

Prefixes	UNIT	ABBREVIATION
deci- one-tenth $1/10$ 0.1 10^{-1}		(d)
centi- one-hundredth $1/100$ 0.01 10^{-2}		(c)
milli- one thousandth $1/1000$ 0.001 10^{-3}		(m)
micro- one-millionth $1/1,000,000$ 0.000001 10^{-6}		(μ)*
Units of length		
1 meter (m)	= 10 decimeters (dm)	= 100 centimeters (cm)
1 centimeter (cm)	= 10^{-2} m	= 10 millimeters (mm)
1 millimeter (mm)	= 10^{-3} m = 10^{-1} cm	= 1000 microns (μ)
1 micron (μ)*	= 10^{-4} m = 10^{-2} cm	= 1000 millimicrons (m μ)
1 millimicron (m μ)	= 10^{-5} m = 10^{-3} cm	= 10 angstroms (A)
1 angstrom (A)	= 10^{-10} m = 10^{-8} cm	= 100 micromicrons ($\mu\mu$)
1 micromicron ($\mu\mu$)	= 10^{-11} m = 10^{-9} cm	
Units of area		
1 square meter (m ²)		= 10,000 square centimeters (cm ²)
1 square centimeter (cm ²)		= 100 square millimeters (mm ²)
1 square millimeter (mm ²)		
Units of volume†		
1 cubic meter (m ³)	=	1,000,000 milliliters (ml)†
1 liter (L)	=	1,000 milliliters (ml)
1 milliliter (ml)	=	1,000 cubic centimeters (cm ³)†
	=	1 cubic centimeter (cm ³)†
1 cubic millimeter (mm ³)	=	1,000 cubic millimeters (mm ³)†
1 cubic micron (μ^3)	=	1,000 cubic microns (μ^3)
Units of mass		
1 kilogram (kg)	=	1,000 grams (gm)
1 gram (gm)	=	1,000 milligrams (mg)
1 milligram (mg) = 10^{-3} gm	=	1,000 micrograms (μ g)
1 microgram (μ g)† = 10^{-6} gm	=	1,000,000 micromicrograms ($\mu\mu$ g)†
1 micromicrogram ($\mu\mu$ g)† = 10^{-12} gm		
Units of concentration		
1 mole per liter (M/L) = M_m gm in 1 L (see footnote§)		
1 millimole per liter (mM/L) = $1/1000$ M/L = 10^{-3} M/L		
1 equivalent per liter (eq/L) = M_a gm/valence in 1 L = 10^{-3} eq/L (see footnote§ and Table 2)		
1 milliequivalent per liter (meq/L) = $1/1000$ equivalent per liter = 10^{-3} eq/L		
1 gram per liter (gm/L) = 1,000 milligrams per liter (mg/L)		
1 milligram per liter (mg/L) = 10^{-3} gm/L = 1,000 micrograms per liter (μ g/L)		
1 microgram per liter (μ g/L) = 10^{-6} gm/L = 1,000,000 micromicrograms per liter ($\mu\mu$ g/L)		
1 micromicrogram per liter ($\mu\mu$ g/L) = 10^{-12} gm/L		

* μ is the Greek letter mu. When used alone it means 1 micron; when used as a prefix it means micro-

†Note that some of these relations are only approximate; these are indicated by the sign \approx . True equality is indicated by the sign =. Note that 1 liter is exactly equal to 1000 ml but not exactly equal to 1000 cm³ (see text). The abbreviation cm³ replaces cc.

‡The terms gamma (γ) for microgram and gamma gamma ($\gamma\gamma$) for micromicrogram, have been used but are not recommended since they add confusion and offer no advantage over the standard nomenclature in which μ (mu) indicates one millionth of a meter (micron), μ g indicates one microgram (millionth of a gram) and $\mu\mu$ g indicates one micromicrogram (one million millionth of a gram).

§Note that molecular weight M_m and atomic weight M_a are both pure numbers; see Table 2 for examples using the atomic weight of electrolytes. In physical chemistry molal solutions are used; a molal solution contains 1 gram molecular weight (M_m gm) of solute dissolved in 1000 gm (not ml) of solvent. Thus a 0.2 molal solution contains 0.2 M_m gm of solute per 1000 gm of solvent.

tests have become "routine" because they have proved to give basic information rapidly and inexpensively in the screening of a large number of

occult blood and serologic test for syphilis. As will be discussed in a separate communication, the red-cell count is not recommended as a routine screening procedure.

The choice of laboratory examinations is usually based on symptoms, signs or laboratory data that

*Adapted from *A Syllabus of Laboratory Examinations in Clinical Diagnosis* (in press) by permission of the Harvard University Press.
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indicate a presumptive value for the performance of a particular test or group of tests. The use of each laboratory test is based on a knowledge, first, of the clinical indication for performing the test, the nature of the test and the diagnostic significance of the results. Three particular aspects of laboratory examinations are considered in the material presented below — namely, certain units of measure of clinical data, the cost to the patient and the degree of accuracy that is required of a laboratory

indicates a reciprocal, $10^{-3} = 1/10^3 = 1/1000 = 0.001$, $2.65 \times 10^{-6} = 2.65 \times 0.000001 = 0.00000265$. The red-cell count in millions per cubic millimeter may be expressed, for example, as $5.34 \times 10^6/\text{mm}^3$, the white-cell count in thousands per cubic millimeter may be expressed, for example, as $8.23 \times 10^3/\text{mm}^3$ (see Table 6).

Expression of the concentration of *electrolytes* of plasma, serum and extracellular fluids has caused confusion. Ions are usually expressed in terms of

TABLE 2 Normal Values for Electrolytes of Human Serum and Plasma Expressed in Milligrams per 100 ml and Converted to Milliequivalents per Liter as Modified from Gamble[†]

Ion	Normal Values*	Atomic Weight	Valence	Conversion of Concentration C in mg/100 ml to meq/L		Normal Value
	(mg/100 ml)			M_a	V	
Cations						
Na ⁺	313-335	23	1	($C \times 10/23$)	$\times 1 = 0.435$	136-145
K ⁺	14-19	39	1	($C \times 10/39$)	$\times 1 = 0.257$	3.5-5.0
Ca ⁺⁺	9.0-10.5	40	2	($C \times 10/40$)	$\times 2 = 0.5$	4.5-5.3
Mg ⁺⁺	1.2-2.4	24	2	($C \times 10/24$)	$\times 2 = 0.833$	1-2
Total						145-157
Anions						
HCO ₃ ⁻ (CO ₂ /vol %)	58-62			1/2 224	$= 0.455$	26-28
Cl ⁻	349-371	35	1	($C \times 10/35$)	$\times 1 = 0.286$	100-106
H ₂ PO ₄ ⁻ (mgP)	3-4.5	31	1.8‡	($C \times 10/31$)	$\times 1.8 = 0.58$	2-3
SO ₄ ⁼ (mgS)	1.6-2.4	31	2	($C \times 10/32$)	$\times 2 = 0.625$	1.0-1.5
Protein (gm/100 ml)	6.5-8.0				2.45‡	16-19
Total						145-157

*Normal values for blood plasma and serum.[‡]

†1 millimole per liter (or 1 milliequivalent per liter) of CO₂ under standard conditions (760 mm-of mercury and 0°C) occupies 22.26 ml or 1 milliequivalent per 100 ml occupies 2.22 ml. Therefore the content (volume) of CO₂ in milliliters per 100 ml of serum (CO₂/volume per cent) when divided by 2.22 gives CO₂ in milliequivalents per liter.

‡As stated by Gamble, the valence of HPO₄ is taken as 1.8 because at the normal pH of extracellular fluid 20 per cent of the concentration of this radical carries 1 equivalent of base (BH₂PO₄) and 80 per cent 2 equivalents (B₂HPO₄). B representing univalent base. Base equivalence per unit of (HPO₄) is therefore 0.2 — (0.8 × 2) = 1.8. The double valency sign is thus small extent inaccurate.

§Derived by titration of the base that is bound by proteins of normal serum at pH 7.35.

procedure so that the results may be significant in establishing an aspect of the diagnosis or treatment.

CERTAIN UNITS OF MEASURE (METRIC SYSTEM)

The physician is called upon to interpret data expressed in units of measure that vary greatly in magnitude. Thus, a patient weighing 70 kg may have a blood volume of 5 liters, a nonprotein nitrogen of 20 mg per 100 milliliters of blood, a blood sodium of 140 milliequivalents per liter, a serum iodine (protein bound) of 4 micrograms per 100 milliliters and a mean corpuscular hemoglobin (for the red cells) of 30 micromicrograms. The shift from micromicrograms to kilograms or from milliequivalents per liter to milligrams per 100 milliliters frequently results in confusion. In Table 1, the usual units of measure in the metric system are arranged in descending order of magnitude, with their abbreviations* and equivalents.

The writing of large or small numbers is facilitated by the use of powers of ten. Thus, 1,000,000 = 10⁶, 1034 = 1.034 × 10³. A negative exponent in-

their chemical equivalence, by the statement of their concentration in milliequivalents per liter, rather than in milligrams or grams per 100 ml. As shown in Tables 1 and 2, the conversion to milliequivalents per liter, for the individual ions, is given by the formula

$$\text{Concentration (meq/L)} = \frac{\text{Concentration (mg/100 ml)} \times 10}{M_a} \times V,$$

where V is the valence and M_a is the atomic weight. The normal values and the formulas for conversion to milliequivalents per liter are shown in Table 2.

It may be remarked that the *unit of volume* used in chemical and biologic work is the *liter*, which is the volume of 1 kg of pure water at the temperature of maximum density, 4°C, and under a pressure equivalent to 760 mm of mercury. It was intended by the constructors of the metric system that the kilogram should be the mass of 1 cubic decimeter (10⁻³ m³) of pure water under these conditions of temperature and pressure, but later, more accurate measurements showed that they had made an error, and the kilogram is now taken as the mass of the international prototype kilogram — a block of metal kept at the International Bureau of Weights

*It will be noted that periods and other punctuations are not used after any abbreviation following the practice of the *Handbook of Chemistry and Physics*. Thirtieth edition. Cleveland: Chemical Rubber Publishing Co., 1948. Pp. 2637-2649. Also the abbreviation of gram or grams is taken as (gm) rather than (gms); similarly milligram or milligrams is abbreviated (mg) rather than (mgm) or (mgms).

TABLE 3 *Examples of Charges Made for Certain Laboratory Examinations (1949)*

EXAMINATION	CHARGES BY FOUR DIFFERENT HOSPITALS*			
	(1) \$	(2) \$	(3) \$	(4) \$
Hematology				
White-cell count	2 00	1 00	1 00	1 00
White-cell count and differential	3 00	2 00	2 00	2 50
Complete blood count	5 50	4 00	4 00	4 00
Anemia unit Complete blood count, hematocrit hemoglobin MCV MCHC MCH reticulocyte count			2 00† or 6 00†	5 00
Platelet or reticulocyte count	3 00	2 00	2 00	2 00
Examination for malarial parasites	3 00	3 00	2 00	2 00
Hematocrit	1 00	2 00	1 50	1 50
Osmotic fragility of red cells			5 00	7 00
Sedimentation rate	2 00	2 00	2 00	2 00
Bleeding time, coagulation time platelet count	2 00	4 50	3 00	4 00
Prothrombin time	2 50	2 00	3 00	3 00
Hemorrhagic disease unit bleeding time clotting time clot retraction platelet count, prothrombin time			5 00	8 00
Blood grouping ABO	2 50			2 00
Blood grouping ABO and Rh	5 00	2 00	3 00	2 50
Rh grouping	2 50	2 00		
Cross matching	2 50			
Blood chemistry				
Sugar	5 00	2 00	3 00	3 00
Glucose tolerance test	15 00	5 00	7 50	2 50†
Urea nitrogen or nonprotein nitrogen	5 00	3 00	3 00	4 00
Chloride	5 00	2 00	2 00	4 50
Total protein copper sulfate method	2 50			6 00
Albumin and globulin concentrations	10 00	7 00	5 00	9 50
Cholesterol	5 00	3 00	4 00	6 00
Icteric index	2 50		1 00	1 50
Bilirubin, direct and indirect	5 00	3 00	3 00	4 00
Bromsulphalein test	2 50	3 00	3 00	2 00
Uric acid	5 00	3 00	4 00	4 00
Creatinine	5 00	2 00	3 00	2 00
Sodium		3 00	10 00	4 00
Calcium	5 00	4 00	5 00	6 50
Phosphorus	5 00	2 00	3 00	4 00
Phosphatase (alkaline)	5 00	5 00	5 00	5 00
Calcium phosphorus and phosphatase	10 00			13 50
Acid phosphatase	5 00	5 00	5 00	5 00
Carbon dioxide combining power	10 00	2 00	4 00	4 00
Liver-function tests				
Serum bilirubin quantitative urobilinogen in the urine bromsulphalein cephalin flocculation, thymol turbidity alkaline phosphatase and serum protein with albumin and globulin			12 00	15 00
Urinalysis				
Urinalysis (specific gravity pH color proteins sugar sediment)	1 50	1 00	1 00	1 50
Quantitative sugar	3 00	1 00	1 00	1 50
Phenolsulfonephthalein	3 00	2 00	2 00	4 00
Urobilinogen, 2 hr sample		1 00		
Renal-function unit nonprotein nitrogen concentration test (Fishberg) phenolsulfonephthalein (intravenous)		7 50	3 00	10 00
Urea clearance			7 50	
Feces				
Inspection, test for occult blood, screening for parasites	2 00	3 00	3 00	1 50
Examination for parasites and ova	5 00	5 00	2 00	1 50
Quantitative fat		5 00	7 50	
Urobilinogen, qualitative		1 00	1 00	1 00
Spinal fluid				
White-cell count	1 50			1 50
Test for globulins	1 00			1 50
Total protein	3 00	7 50	7 00	2 50
Gold sol curve	5 00			2 50
Wassermann	5 00			8 00
Spinal-fluid complete smear culture white-cell count differential qualitative protein	5 00	5 00	5 00	
Gastric analysis				
			25 00	20 00
Miscellaneous				
Frozen section consultation	7 50	7 50	10 00	10 00
Electrocardiogram (usual leads)	15 00	20 00		9 00
Electrocardiogram (16 leads)	7 50	5 00	7 50	4 00†
Basal metabolism			9 00	8 00
Friedman or Aschheim-Zondek test for pregnancy	7 50	5 00		10 00
Test for follicle stimulating hormone		7 50		10 00
Test for 17 ketosteroids		5 00	3 00	13 50
Blood culture	10 00	7 50		13 50
Inoculation of guinea pig for tuberculosis	6 00	2 00		2 50
Sputum for tubercle bacilli		3 00		6 50
Papanicolaou smear	5 00	3 00	4 00	2 50
Blood Wassermann (rapid test)	5 00	5 00		7 00 one
Antibiotic sensitivity				10 00 two
X-ray				
Chest, stereo (with fluoroscopy)	15 00	15 00	15 00	15 00
Gastrointestinal series with 6-hr film	25 00	15 00	25 00	15 00
Barium enema	15 00	15 00	17 50	20 00
Gall-bladder test	15 00	10 00	20 00	20 00
Intravenous pyelogram	25 00	15 00	25 00	15 00
Retrograde pyelogram		15 00	20 00	15 00
Bone series			10 00	
Skull anterior posterior lateral		10 00	20 00	20 00
Ventriculogram		15 00		15 00
Maximum charge for all laboratory examinations		50 00		

* (1) Stanford University Hospitals San Francisco California (rates for private patients)
 (2) Baker Memorial Massachusetts General Hospital Boston Massachusetts Maximum charge for total laboratory fees \$50 00 (rates for private patients)

(3) Faulkner Hospital Boston Massachusetts (rates for private patients)
 (4) A teaching hospital in Philadelphia Pennsylvania (rates for semiprivate patients)
 †Complete blood count included in routine charge for inpatients The charge of \$6 is for an outpatient.
 ‡For each determination
 §Repeat test.

and Measures near Paris, it is equal to the mass of $0.001000027 \text{ m}^3 (= 1.000027 \text{ dm}^3)$ of water. Consequently, $1 \text{ ml} = 1.000027 \text{ cm}^3$, but the mass of 1 ml of pure water under the conditions specified is exactly 1 gm . For these reasons the milliliter (ml) is substituted for the more familiar cubic centimeter (cm^3)* as a unit of volume.

For convenience and clarity in expression, units that avoid the use of large numbers or large fractions are chosen when possible. For example, a patient's weight of $70,000 \text{ gm}$ is expressed as 70 kg , a dosage of vitamin B_{12} is more conveniently expressed as $15 \mu\text{g}$ (micrograms) than 0.015 mg or 0.000015 gm or $15 \times 10^{-6} \text{ gm}$, a concentration of potassium in the serum is expressed as 5 milliequivalents per liter (meq/L) rather than 0.005 equivalent per liter (eq/L). The expression "milligrams per cent (mg %)" has caused confusion since, literally, it means the number of milligrams per 100 parts—that is, per 100 mg—and not per 100 cm^3 or per 100 ml, as is usually implied. Accordingly, the expression "milligrams per cent" should be abandoned, and units that are determinate should be used, such as mg/100 ml or mg/L. Thus, the concentration of nonprotein nitrogen in whole blood is expressed as $30 \text{ mg}/100 \text{ ml}$, rather than $0.03 \text{ gm}/100 \text{ ml}$ and not as 30 mg \% .

CURRENT COST OF LABORATORY EXAMINATIONS AND CERTAIN LABORATORY APPARATUS

Unfortunately, laboratory examinations cost money because of the time, skill, reagents, apparatus, and building space required for their proper performance. The increasing number and cost of laboratory procedures required for proper diagnosis and treatment presents a significant economic problem in the care of the patient. There is no doubt that well controlled laboratory examinations are essential, but because they are expensive, they should be ordered with care, done with proper accuracy and interpreted critically. Laboratory examinations are obviously subject to abuses. It may be improper for a patient to pay for extra laboratory examinations that are performed primarily for teaching or research purposes. A more serious error may result from the failure to perform the proper kind or number of tests because of cost to the patient. It is probably essential that the patient be instructed in the need, cost and value of laboratory examinations in his particular case just as he is informed of the need, cost, and value of treatment with an antibiotic or by an operative procedure.

No figures are available on the true costs of laboratory procedures. In place of a cost analysis, the current charges made for certain laboratory tests in different parts of the country are listed in Table 3. At one hospital (No 3 in Table 3) for private patients a flat laboratory fee is charged to each patient to cover routine laboratory work.

*The cubic centimeter—as with other volumes expressed as the cube is abbreviated as (cm^3) rather than the more familiar (cc).

required of all who are admitted. Since the routine varies on different services, the fees charged are as follows: medical patients, \$9.00, surgical patients, \$6.00, obstetric patients, \$4.00. The charges cover blood counts, urinalysis and certain other procedures. Other tests are charged for separately (see column 3, Table 3). All charges are based on a unit system in which each unit is valued at \$0.50,

TABLE 4 Equipment Used for Clinical Laboratory Procedures

ITEMS	UNIT PRICE (1949) \$
Monocular microscope with oil immersion objective (complete)	299.00
Test tubes and holders*	
Test tubes 20 x 150 mm	0.07
Centrifuge tube, 15 ml soft glass ungraduated	0.10
Centrifuge tube 15 ml graduated	0.86
Centrifuge tube, 15 ml, Addison or Sherky-Stafford	1.34
Test tube brush	0.07
Test tube holder wire	0.12
Test tube rack	1.20
Pipettes*	
10 ml Mohr	0.97
1 ml, serological	0.75
0.10 ml micro for Folin sugar method	1.00
0.02 ml for Sahli hemoglobinometer	1.00
Hematocrit pipette with rubber bulb	0.30
Vessels*	
Cylinder 50 ml graduated	1.10
Beaker, 250 ml pyrex	0.25
Flask, Erlenmeyer 250 ml pyrex	0.32
Evaporating dish porcelain	1.70
Wine glass	0.40
Screw cap jar	0.15
Unnometer 50 ml cylinder ungraduated	0.80
hydrometer	0.61
Funnel, 2 1/2 in. diameter	0.40
Dropping bottle rubber bulb	0.10
Ironware*	
Tripod	0.84
Wire gauze with asbestos 5 in.	0.12
Bunsen burner	0.57
Clinical model centrifuge (International Equipment Company)	105.00
Hemoglobinometry*	
Tallqvist hemoglobin scale (book)	1.00
Sahli (Hellige hemoglobinometer)	18.00
Haden-Hansen (clinical model)	19.05
Spencer hemoglobinometer (American Optical Company)	38.00
Transformer	15.00
Evelyn macro-photoelectric cell colorimeter (complete)	385.00
Klett-Summerson photoelectric cell colorimeter	171.00
Wintrobe tubes*	1.10
Water bath, constant temperature (37°–60° C) with racks	100.00
Syringes, needles and carriers*	
10 ml	3.25
30 ml	4.50
50 ml	7.00
Syringe carriers	0.50
Hypodermic needles 19 gage	0.25
Hypodermic needles 20 gage	0.25
Hypodermic needles 22 gage	0.25
Blood trays*	5.00
Sedimentation racks Wintrobe method	10.00
Sedimentation rack, Westergren 6 tube	16.50
Tubes sedimentation Westergren	0.97
Comparator block and icteric index standards	12.60

*Unit prices given apply when items are purchased in lots of 1 dozen.

as recommended by the New England Pathological Society in unpublished data.

Certain tests have been grouped together into units such as those related to anemia, hemorrhagic disease, liver function and kidney function. In these instances, charges are kept to a minimum and scaled to the patient's income to encourage the use of these groups of procedures in diagnosis.

The cost of equipment necessary for performing certain of the basic clinical laboratory examinations is listed in Table 4.

TABLE 3 *Examples of Charges Made for Certain Laboratory Examinations (1949)*

EXAMINATION	CHARGES BY FOUR DIFFERENT HOSPITALS*			
	(1) \$	(2) \$	(3) \$	(4) \$
Hematology				
White-cell count	2 00	1 00	1 00	1 00
White-cell count and differential	3 00	2 00	2 00	2 50
Complete blood count	5 50	4 00	4 00	4 00
Anemia unit Complete blood count, hematocrit, hemoglobin MCV MCHC MCH reticulocyte count			2 00† or 6.00†	5 00
Platelet or reticulocyte count	3 00	2 00	2 00	2 00
Examination for malarial parasites	3 00	3 00	2 00	2 00
Hematocrit	1 00	2 00	1 50	1 50
Osmotic fragility of red cells			5 00	7 00
Sedimentation rate	2 00	2 00	2 00	2 00
Bleeding time, coagulation time platelet count	2 00	4 50	3 00	4 00
Prothrombin time	2 50	2 00	1 00	3 00
Hemorrhagic disease unit bleeding time clotting time clot retraction platelet count			5 00	8 00
prothrombin time				2 00
Blood grouping ABO	2 50		1 00	2 50
Blood grouping ABO and Rb	5 00	2 00		
Rb grouping	2 50	2 00		
Cross matching	2 50			
Blood chemistry				
Sugar	5 00	2 00	3 00	3 00
Glucose tolerance test	15 00	5 00	7 50	2 50†
Urea nitrogen or nonprotein nitrogen	5 00	3 00	3 00	4 00
Chloride	5 00	2 00	2 00	4 50
Total protein copper sulfate method	2 50			6 00
Albumin and globulin concentrations	10 00	7 00	5 00	9 50
Cholesterol	5 00	3 00	4 00	6 00
Icteric index	2 50		1 00	1 50
Bilirubin, direct and indirect	5 00	3 00	3 00	4 00
Bromsulphalein test	2 50	3 00	4 00	4 00
Urine acid	5 00	3 00	3 00	2 00
Creatinine	5 00	2 00	10 00	4 00
Sodium	3 00		5 00	6 50
Calcium	5 00	4 00	5 00	4 00
Phosphorus	5 00	2 00	5 00	5 00
Phosphatase (alkaline)	5 00	5 00		13 50
Calcium phosphorus and phosphatase	10 00		5 00	5 00
Acid phosphatase	5 00	5 00	5 00	4 00
Carbon dioxide combining power	10 00	2 00	4 00	
Liver-function tests				
Serum bilirubin quantitative urobilinogen in the urine bromsulphalein cephalin flocculation thymol turbidity alkaline phosphatase and serum protein with albumin and globulin			12 00	15 00
Urinalysis				
Urinalysis (specific gravity pH color proteins, sugar sediment)	1 50	1 00	1 00	1 50
Quantitative sugar	3 00	1 00	1 00	1 50
Phenolsulphobalein	3 00	2 00	2 00	4 00
Urobilinogen, 2 hr sample		1 00		
Renal-function unit nonprotein nitrogen concentration test (Fisberg) phenolsulphobalein (intravenous)		7 50	3 00	10 00
Urea clearance			7 50	
Feces				
Inspection, test for occult blood screening for parasites	2 00	3 00	3 00	1 50
Examination for parasites and ova	5 00	5 00	2 00	1 50
Quantitative fat		5 00	7 50	
Urobilinogen, qualitative		1 00	1 00	1 00
Spinal fluid				
White-cell count	1 50			1 50
Test for globulins	1 00			1 50
Total protein	3 00	7 50	7 00	2 50
Gold-sol curve	5 00			2 50
Wassermann	5 00			8 00
Spinal-fluid complete smear culture white-cell count differential qualitative protein	5 00	5 00	5 00	
Gastric analysis				
			25 00	20 00
Miscellaneous			10 00	10 00
Frozen section consultation	7 50	7 50		
Electrocardiogram (usual leads)	15 00	20 00		
Electrocardiogram (16 leads)	7 50	5 00	7 50	9 00
Basal metabolism				4 00†
			9 00	8 00
Friedman or Aschheim-Zondek test for pregnancy	7 50	5 00		10 00
Test for follicle-stimulating hormone		7 50		10 00
Test for 17 ketosteroids		5 00		13 50
Blood culture	6 00	5 00	1 00	13 50
Inoculation of guinea pig for tuberculosis	10 00	7 50		2 50
Sputum for tubercle bacilli	6 00	2 00		2 50
Papanicolaou smear		3 00	4 00	6 50
Blood Wassermann (rapid test)	5 00	2 00		2 50
Antibiotic sensitivity	5 00	5 00		7 00 one two
				10 00 two
X-ray				
Chest, stereo (with fluoroscopy)	15 00	15 00	15 00	15 00
Gastrointestinal series with 6-hr film	25 00	15 00	25 00	15 00
Barium enema	15 00	15 00	17 50	20 00
Gall-bladder test	15 00	10 00	20 00	20 00
Intravenous pyelogram	25 00	15 00	20 00	15 00
Retrograde pyelogram			10 00	15 00
Bone series			20 00	20 00
Skull anterior posterior lateral		10 00		15 00
Ventriculogram		15 00		
Maximum charge for all laboratory examinations		50 00		

* (1) Stanford University Hospitals, San Francisco, California (rates for private patients)
 (2) Baker Memorial, Massachusetts General Hospital, Boston, Massachusetts (Maximum charge for total laboratory fees \$50.00 (rates for private patients))

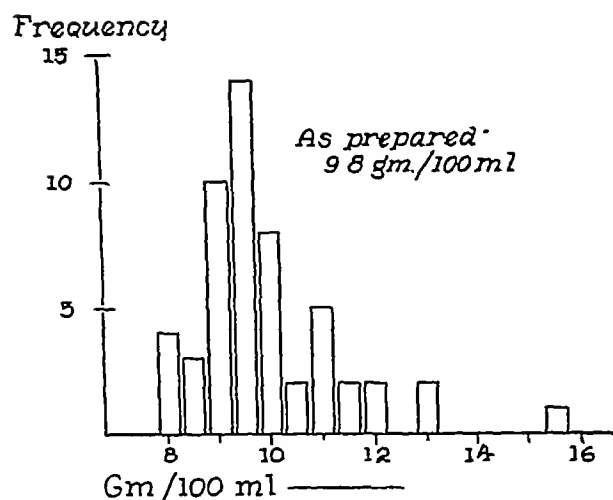
(3) Faulkner Hospital, Boston, Massachusetts (rates for private patients)
 (4) A teaching hospital in Philadelphia, Pennsylvania (rates for semiprivate patients)

† Complete blood count included in routine charge for inpatients. The charge of \$6 is for an outpatient.

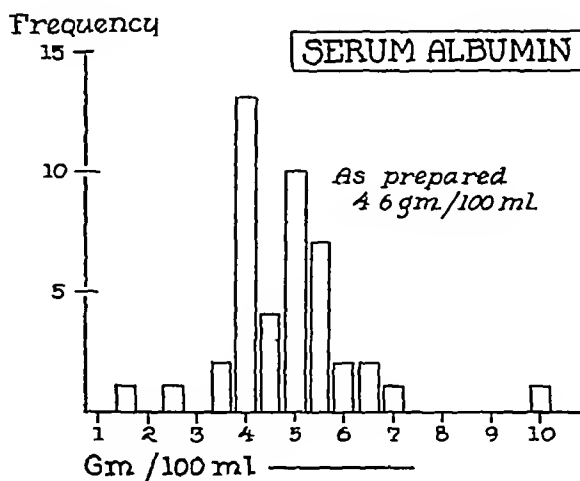
‡ For each determination

§ Repeat test.

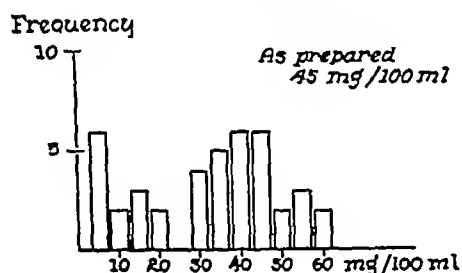
HEMOGLOBIN



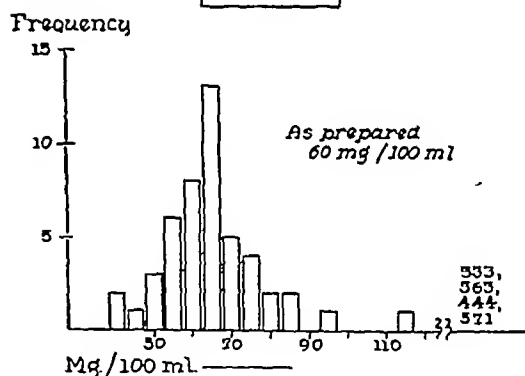
SERUM ALBUMIN



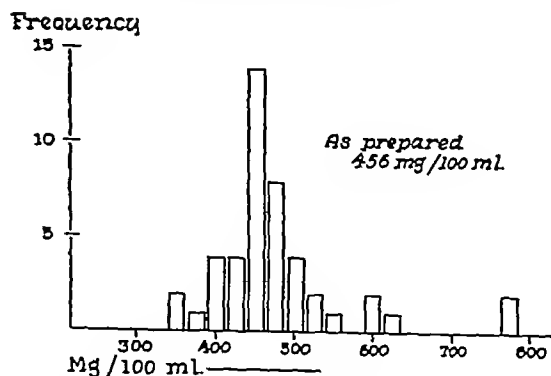
UREA



GLUCOSE



SODIUM CHLORIDE



CALCIUM

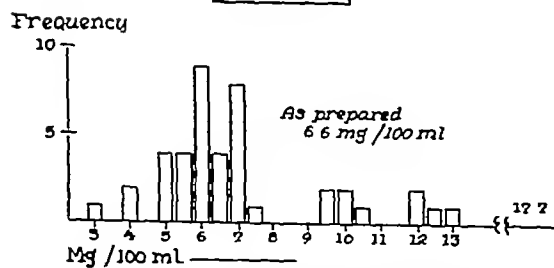


FIGURE 1 Frequency Distribution of Results Obtained in Different Laboratories on Samples of the Same Known Solution (Reproduced from Belk and Sunderman,⁴ by Permission of the Publisher)
Half the published data are shown in the figure and are representative of the whole

QUANTITATIVE EVALUATION OF DATA

With the enormous increase in the number of laboratory examinations that can be made, the physician is called upon continuously to evaluate data in a scientific manner—that is, to know the limits of significance of the results quantitatively and clinically. Quite properly, the physician wishes to obtain a maximum of reliable information on which to base a diagnosis, and to obtain it at minimum cost in minimum time and as simply as possible. Accordingly, there will always be a high priority in clinical medicine for the development of *screening examinations* that will indicate the presence or absence of disease in a rapid, reliable and inexpensive manner. The data required may be qualitative, semiquantitative or, in certain instances, precisely quantitative to be of proper use to the physician in diagnosis and treatment. Again, the physician balances the potential value of a test against its cost, but gives first priority to the clinical indication for the procedure.

In general, costs rise with the degree of accuracy required, since precision usually requires more time of highly skilled personnel* and more equipment than qualitative or semiquantitative examinations. Accordingly, the physician will be alert to know the degree of accuracy required and to interpret data with a full knowledge of their limitations in specificity and limits of error. For example, the determination of plasma fibrinogen, serum albumin and serum globulin requires skill in the use of the Kjeldahl method of nitrogen analysis, these determinations inevitably are expensive. If the procedures are done by unskilled workers, the data are erroneous, not reproducible and so misleading clinically as to be useless and treacherous (see Fig 1 for serum albumin). Accordingly, certain screening examinations for plasma proteins that are rapid, inexpensive and semiquantitative have an important place as diagnostic procedures. For example, if the total protein is normal as measured by the copper sulfate method, if the serum globulins are normal as indicated by the formol-gel reaction and if the plasma fibrinogen and serum globulins are normal as indicated by the sedimentation rate, plasma protein fractions may be considered normal, and its quantitative determination is not essential for diagnosis.

It is emphasized, immediately, that it may be as fallacious and wasteful to use a refined quantitative procedure when qualitative results suffice as it is to attempt the evaluation of data of qualitative significance when precise information is necessary. Accordingly, a knowledge of the limits of accuracy of the data is an integral part of their diagnostic

*Fortunately, there are occasional exceptions. For example, the hematocrit can be determined with remarkable accuracy and in a short time by a trained high school girl equipped with a centrifuge and a dozen Wintrobe tubes. This easy precision results from the admirable features of the method itself. Conversely the red-cell count as a method has an inherent error of chance distribution of cells that requires long labor and great care to overcome (see Table 6).

evaluation. There is no place in medicine for blind faith in a written figure on a patient's chart. Listed below are examples of the wide span of the limits of accuracy of data as applied to diagnosis and treatment.

Qualitative Determinations

An unrefined, and possibly nonspecific, qualitative procedure is frequently of great *value* as a screening procedure or as a true diagnostic method. Thus, the presence of gross blood in urine, feces, vomitus or sputum may require only visual observation for detection, and certainly does not require refined quantitative evaluation to be of important diagnostic value. Similarly, if a patient's vomitus produces a bright-red color with the pH indicator, Töpfer's reagent, this is first-class evidence for the presence of free hydrochloric acid and would immediately exclude a diagnosis of classic Addisonian pernicious anemia. If a patient bleeds indefinitely after an ordinary capillary puncture for the collection of blood, this observation is as eloquent data as may be obtained from a test performed especially for measuring the bleeding time. If the urine becomes solidified when boiled with acetic acid, this test alone requires a presumptive diagnosis of nephrosis. If the hematocrit tube shows a layer of white cells that is 10 mm high, the presumptive diagnosis is leukemia until proved otherwise. If a patient enters the hospital with manifest history and signs of dehydration, the observation that the specific gravity of the urine sample is only 1.010 suggests low concentrating power and abnormal renal function. The passage of a stone into urine or stool is a reliable qualitative datum.

However, qualitative determinations have inevitable *limitations* that require full recognition. For example, the observation of blood in the vomitus, without further information concerning the patient, may not indicate whether the bleeding is of minor nature or of a magnitude that threatens the life of the patient. The passage of a stone in the urine does not in itself indicate whether the patient has such an abnormality as a parathyroid tumor, excessive ingestion of alkali or a congenital defect in the metabolism of cystine.

Semiquantitative Determinations

Data of semiquantitative accuracy are frequently as *valuable* as more refined information. This is evidenced by the enormous number of tests, reported in terms of degree of positivity, and expressed as "positive or negative" or positive in terms of "+ to 4+" For example, in a patient with known diabetes, a "brick red" (4+) test with Benedict's qualitative sugar reagent is reliable semiquantitative information, as is a 4+ reaction for acetone bodies. There may be no requirement, in the proper handling of diabetic coma, to determine, in a more quantitative manner, the sugar and acetone bodies in the

of the future will demand information on the limits of significance of the results before he evaluates data in relation to the patient

Statistical Analysis of Certain Data Obtained from Laboratory Examinations of Blood

No attempt is made in this paper to consider statistical methods in general, which are adequately described elsewhere.^{5,11} The discussion here is limited to certain examples of evaluating, by statistical methods, the determinations obtained by about 20 different observers, examining samples of a single specimen of venous blood and using the procedures listed below. Such an exercise can be used to demonstrate the limits of significance of data obtained by different methods and to show improvement in the accuracy of observations resulting from training. The data can then be entered for analysis on a blank form, a portion of which is shown in Table 6. The results shown are typical data obtained by students in training who have already developed considerable proficiency.

Red-cell count The red-cell count is performed in two ways. In the first of these two red-cell

variation, SD , or σ (small sigma). The standard deviation is calculated as follows, using the expressions commonly employed in statistical methods.

The arithmetic average, or mean, M is calculated by obtaining the sum Σ (capital sigma) of the

TABLE 5 Factors Contributing to Technical Inaccuracies and Other Unsatisfactory Conditions in Clinical Laboratories *

FACTOR	No. of Times Listed
Poorly trained technicians	82
Inadequate number of technicians	80
Lack of understanding between pathologist and staff	64
Poor equipment	63
Insufficient floor space	57
Miscellaneous factors (inadequate orderly service, insufficient secretarial service and so forth)	39

*Based on data of Bell and Sunderman.⁴

total number N of observations, each observation being designated by the letter X . Thus,

$$\text{Arithmetic Average or Mean, } M = \frac{\Sigma X}{N}$$

The deviation d of each observation from the mean is calculated by subtraction of the mean from

TABLE 6 Results Obtained by Different Medical Students after Considerable Training in the Examination of Samples of the Same Blood Specimen from a Patient with Cooley's Anemia *

DETERMINATION	NUMBER OF OBSERVATIONS	MAXIMUM	MINIMUM	MEAN (AVERAGE)	TWO STANDARD DEVIATIONS (2 SIGMA)†	TWO COEFFICIENTS OF VARIATION %
Hematocrit (percentage)	10	25.0	23.5	24.1	± 0.84	± 3.4
Hemoglobin (gm/100 ml)						
Photoelectric-cell colorimeter (Evelyn)	9	8.3	7.8	8.0	± 0.36	± 4.5
Spencer hemoglobinometer	17	9.1	8.0	8.7	± 0.78	± 9.0
Sahlb	17	9.7	7.3	8.9	± 1.2	± 14.0
Haden-Hauser	17	8.7	7.5	8.2	± 0.8	± 10.0
Tallqvist	17	9.4	6.5	7.8	± 1.6	± 21.0
Counts of formed elements of blood:						
R. B. C. ($10^6/\text{mm}^3$)						
(2 pipettes, 2 chambers)	20	2.5	2.0	2.2	± 0.36	± 16.0
(1 pipette, 2 chambers)	18	2.4	1.7	2.1	± 0.28	± 13.0
W. B. C. ($10^3/\text{mm}^3$)	18	11.6	7.55	9.1	± 1.83	± 20.0
Reticulocytes wet method (per cent)	19	6.2	2.2	4.0		

*The limits of significance (two coefficients of variations) are representative of the methods themselves and indicate what may be obtained from any laboratory. The small error of the hematocrit and the hemoglobin determined by the photo-electric-cell colorimeter (Evelyn) should be especially noted.

†Units are those of the observations.

pipettes are filled, each being used to fill one counting chamber of a hemacytometer, 400 to 600 cells being counted in each chamber. The results of counts in the two chambers are averaged. Secondly, one red-cell pipette is filled and used to fill both counting chambers of a hemacytometer, the rest of the procedure being carried out as above.

Determination of hemoglobin Five methods are used: the photoelectric-cell colorimeter (Evelyn), Spencer hemoglobinometer (American Optical Company), Sahlb, Haden-Hauser and Tallqvist.

Hematocrit The Wintrobe method is used.

Numerical Expression of the Degree of Deviation of Data, Calculation of the Standard Deviation

It is more convenient to express numerically, rather than graphically, the degree of variation of data, expressing the results as the standard de-

it, $d = X - M$, d may be either positive or negative. The deviation of each observed value is then squared, to give d^2 , and the sum Σd^2 of all the squares is obtained. The mean of the sum of the squares of the deviations $\Sigma d^2/N$ is employed in the finding of σ when N is large, but when the number of observations is small, as in the examples used here, the sum of the squares of the deviation is better divided by $N-1$ (see Fisher⁷). The standard deviation is calculated by determination of the square root of $\Sigma d^2/(N-1)$ — that is,

$$\sigma = \sqrt{\Sigma d^2/(N-1)}$$

An example of the calculation from data for eleven red-cell counts is shown in Table 7.

Interpretation Many biologic measurements tend to follow the so-called *normal distribution*, in which 95 per cent of the observed values fall within the

urine If a spinal tap shows pus cells and a few gram-negative intracellular diplococci, this is presumptive evidence for treatment of the patient for meningococcal meningitis before the bacteriologic examinations have been reported, concerning the fermentation of sugars and the immunologic classifications of the organism If the patient has clinically manifest infectious mononucleosis, the demonstration of 4+ heterophil antibodies in the serum is qualitative and semiquantitative information that has high presumptive value in establishing the diagnosis, treatment of the serum with guinea-pig kidney and the demonstration of nonadsorption of the heterophil antibodies is a further qualitative refinement of confirmatory value In a patient suspected to have liver disease, the finding in the urine of 4+ bile and 4+ color reaction with Ehrlich's aldehyde reagent may be as meaningful in diagnosis as the extraction, qualitative identification and quantitative determination of bilirubin and urobilinogen

The *limitations* of semiquantitative data require as careful recognition as the potential value of such data The greatest abuse in the evaluation of data is the interpretation of semiquantitative results as though they were quantitatively accurate within narrow limits For example, the red-cell count, in unskilled hands, frequently has a limit of significance of ± 20 per cent * The determination of the mean corpuscular volume, therefore, has an error of at least the same order of magnitude However, clinicians may accept the reported mean corpuscular volume at face value in characterizing the size of the red cells Also, there are frequent errors in judgment concerning the interpretation of results of the determination of hemoglobin In this instance, many clinical methods are semiquantitative, as employed, and the reproducibility of results varies within the limits of ± 15 per cent * A physician may report "clinical improvement," using such a method, if two consecutive determinations show a so-called "increase" of 5 per cent, obviously, such a "change" in hemoglobin has no quantitative significance whatsoever

Certain examinations depend upon the *preservation* of such biologic substances as casts or urobilinogen in the urine, bacteria in culture mediums and fixation of biopsy material Semiquantitative determinations made on poorly preserved biologic specimens have inherent errors of significant magnitude that vitiate the results, waste the time of the examiner and may seriously influence diagnosis and treatment of the patient

Quantitative Determinations

The continual addition of quantitative determinations, having known limits of significance, is evidence of the increasing applications of the scientific method in medicine for establishment

of diagnosis and treatment In the field of biochemistry, the clinical *value* of such quantitative determinations is manifest—for example, the measurements of blood sugar, urea, uric acid, calcium and other substances In the biologic field, the determination of hemoglobin by the photoelectric-cell colorimeter and the determination of the hematocrit have made possible results that are reproducible within limits of ± 5 per cent.†

The *limitations* of quantitative determinations in medicine result largely from a failure to appreciate the limits of significance of the particular method, in the hands of the particular examiner, and as determined on a particular sample For example, Belk and Sunderman⁴ sent carefully prepared duplicate samples of known solutions to 59 different laboratories in Pennsylvania for quantitative determinations The range of the results is summarized in Fig 1 It is immediately apparent that many results were grossly wrong, would mislead the physician in establishing a diagnosis and might seriously affect the treatment and, therefore, the life of the patient Belk and Sunderman received opinions from 95 pathologists concerning the causes of unsatisfactory results, these are summarized in Table 5

Sources of error in quantitative determinations A list of sources of error in quantitative determinations in medicine would include at least the following

Objective errors (beyond the control of the examiner)

Sampling error in obtaining a representative sample and in stability, such as preservation, of the biologic specimen

Method errors of measurement, of instruments of assay (specificity, reproducibility)

Subjective errors (within the control of the examiner)

Technical mistakes errors of technical nature as related to quantitative measurement and proper control of the method

Definition of the limits of quantitative significance of data From the above discussion, it is apparent that a qualitative determination may have significance in diagnosis within wide limits of variation of the data The very observation that blood is present in vomitus is a *qualitative datum* that determines the *presence or absence* of a substance The crude observation that the vomitus contains a large, moderate or small amount of blood is a *semiquantitative datum* that has value even though the absolute number of milligrams of hemoglobin in the sample can be given only within wide limits In a quantitative determination, it is necessary to define the significance of the final result if it is to be interpreted properly This is most readily done by one of several statistical methods The physician

*Two coefficients of variation

†Two coefficients of variation

of the future will demand information on the limits of significance of the results before he evaluates data in relation to the patient

Statistical Analysis of Certain Data Obtained from Laboratory Examinations of Blood

No attempt is made in this paper to consider statistical methods in general, which are adequately described elsewhere.⁵⁻¹¹ The discussion here is limited to certain examples of evaluating, by statistical methods, the determinations obtained by about 20 different observers, examining samples of a single specimen of venous blood and using the procedures listed below. Such an exercise can be used to demonstrate the limits of significance of data obtained by different methods and to show improvement in the accuracy of observations resulting from training. The data can then be entered for analysis on a blank form, a portion of which is shown in Table 6. The results shown are typical data obtained by students in training who have already developed considerable proficiency.

Red-cell count The red-cell count is performed in two ways. In the first of these two red-cell

variation, S D, or σ (small sigma). The standard deviation is calculated as follows, using the expressions commonly employed in statistical methods.

The arithmetic average, or mean, M is calculated by obtaining the sum Σ (capital sigma) of the

TABLE 5 *Factors Contributing to Technical Inaccuracies and Other Unsatisfactory Conditions in Clinical Laboratories**

FACTOR	No. of TIMES LISTED
Poorly trained technicians	82
Inadequate number of technicians	80
Lack of understanding between pathologist and staff	64
Poor equipment	63
Insufficient floor space	57
Miscellaneous factors (Inadequate orderly service, insufficient secretarial service and so forth)	39

*Based on data of Belk and Sunderman.⁴

total number N of observations, each observation being designated by the letter X . Thus,

$$\text{Arithmetic Average or Mean, } M = \frac{\Sigma X}{N}$$

The deviation d of each observation from the mean is calculated by subtraction of the mean from

TABLE 6 *Results Obtained by Different Medical Students after Considerable Training in the Examination of Samples of the Same Blood Specimen from a Patient with Cooley's Anemia**

DETERMINATION	NUMBER OF OBSERVATIONS	MAXIMUM	MINIMUM	MEAN (AVERAGE)	TWO STANDARD DEVIATIONS (2 SIGMA)†	TWO COEFFICIENTS OF VARIATION %
Hematocrit (percentage)	10	25.0	23.5	24.1	± 0.84	± 3.4
Hemoglobin (gm/100 ml)						
Photoelectric-cell colorimeter (Evelyn)	9	8.3	7.8	8.0	± 0.36	± 4.5
Spencer hemoglobinometer	17	9.1	8.0	8.7	± 0.78	± 9.0
Sahli	17	9.7	7.3	8.9	± 1.2	± 14.0
Haden-Hauser	17	8.7	7.3	8.2	± 0.8	± 10.0
Tallqvist	17	9.4	6.5	7.8	± 1.6	± 21.0
Counts of formed elements of blood						
R. B. C. ($10^6/\text{mm}^3$)						
(2 pipettes, 2 chambers)	20	2.5	2.0	2.2	± 0.36	± 16.0
(1 pipette, 2 chambers)	18	2.4	1.7	2.1	± 0.28	± 13.0
W. B. C. ($10^3/\text{mm}^3$)	18	11.6	7.55	9.1	± 1.83	± 20.0
Reticulocytes, wet method (per cent)	19	6.2	2.2	4.0		

*The limits of significance (two coefficients of variations) are representative of the methods themselves and indicate what may be obtained from any laboratory. The small error of the hematocrit and the hemoglobin determined by the photo-electric-cell colorimeter (Evelyn) should be especially noted.

†Units are those of the observations.

pipettes are filled, each being used to fill one counting chamber of a hemacytometer, 400 to 600 cells being counted in each chamber. The results of counts in the two chambers are averaged. Secondly, one red-cell pipette is filled and used to fill both counting chambers of a hemacytometer, the rest of the procedure being carried out as above.

Determination of hemoglobin Five methods are used: the photoelectric-cell colorimeter (Evelyn), Spencer hemoglobinometer (American Optical Company), Sahli, Haden-Hauser and Tallqvist. **Hematocrit** The Wintrobe method is used.

Numerical Expression of the Degree of Deviation of Data Calculation of the Standard Deviation

It is more convenient to express numerically, rather than graphically, the degree of variation of data, expressing the results as the standard de-

it, $d = X - M$, d may be either positive or negative. The deviation of each observed value is then squared, to give d^2 , and the sum Σd^2 of all the squares is obtained. The mean of the sum of the squares of the deviations $\Sigma d^2/N$ is employed in the finding of σ when N is large, but when the number of observations is small, as in the examples used here, the sum of the squares of the deviation is better divided by $N-1$ (see Fisher⁷). The standard deviation is calculated by determination of the square root of $\Sigma d^2/(N-1)$ — that is,

$$\sigma = \sqrt{\Sigma d^2/(N-1)}$$

An example of the calculation from data for eleven red-cell counts is shown in Table 7.

Interpretation Many biologic measurements tend to follow the so-called *normal distribution*, in which 95 per cent of the observed values fall within the

urine If a spinal tap shows pus cells and a few gram-negative intracellular diplococci, this is presumptive evidence for treatment of the patient for meningococcal meningitis before the bacteriologic examinations have been reported, concerning the fermentation of sugars and the immunologic classifications of the organism If the patient has clinically manifest infectious mononucleosis, the demonstration of 4+ heterophil antibodies in the serum is qualitative and semiquantitative information that has high presumptive value in establishing the diagnosis, treatment of the serum with guinea-pig kidney and the demonstration of nonadsorption of the heterophil antibodies is a further qualitative refinement of confirmatory value In a patient suspected to have liver disease, the finding in the urine of 4+ bile and 4+ color reaction with Ehrlich's aldehyde reagent may be as meaningful in diagnosis as the extraction, qualitative identification and quantitative determination of bilirubin and urobilinogen

The *limitations* of semiquantitative data require as careful recognition as the potential value of such data The greatest abuse in the evaluation of data is the interpretation of semiquantitative results as though they were quantitatively accurate within narrow limits For example, the red-cell count, in unskilled hands, frequently has a limit of significance of ± 20 per cent * The determination of the mean corpuscular volume, therefore, has an error of at least the same order of magnitude However, clinicians may accept the reported mean corpuscular volume at face value in characterizing the size of the red cells Also, there are frequent errors in judgment concerning the interpretation of results of the determination of hemoglobin In this instance, many clinical methods are semiquantitative, as employed, and the reproducibility of results varies within the limits of ± 15 per cent * A physician may report "clinical improvement," using such a method, if two consecutive determinations show a so-called "increase" of 5 per cent, obviously, such a "change" in hemoglobin has no quantitative significance whatsoever

Certain examinations depend upon the *preservation* of such biologic substances as casts or urobilinogen in the urine, bacteria in culture mediums and fixation of biopsy material Semiquantitative determinations made on poorly preserved biologic specimens have inherent errors of significant magnitude that vitiate the results, waste the time of the examiner and may seriously influence diagnosis and treatment of the patient

Quantitative Determinations

The continual addition of quantitative determinations, having known limits of significance, is evidence of the increasing applications of the scientific method in medicine for establishment

of diagnosis and treatment In the field of biochemistry, the clinical *value* of such quantitative determinations is manifest—for example, the measurements of blood sugar, urea, uric acid, calcium and other substances In the biologic field, the determination of hemoglobin by the photoelectric cell colorimeter and the determination of the hematocrit have made possible results that are reproducible within limits of ± 5 per cent.†

The *limitations* of quantitative determinations in medicine result largely from a failure to appreciate the limits of significance of the particular method, in the hands of the particular examiner, and as determined on a particular sample For example, Belk and Sunderman⁴ sent carefully prepared duplicate samples of known solutions to 59 different laboratories in Pennsylvania for quantitative determinations The range of the results is summarized in Fig 1 It is immediately apparent that many results were grossly wrong, would mislead the physician in establishing a diagnosis and might seriously affect the treatment and, therefore, the life of the patient Belk and Sunderman received opinions from 95 pathologists concerning the causes of unsatisfactory results, these are summarized in Table 5

Sources of error in quantitative determinations A list of sources of error in quantitative determinations in medicine would include at least the following

Objective errors (beyond the control of the examiner)

Sampling error in obtaining a representative sample and in stability, such as preservation, of the biologic specimen

Method errors of measurement, of instruments of assay (specificity, reproducibility)

Subjective errors (within the control of the examiner)

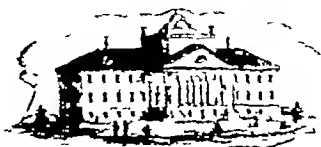
Technical mistakes errors of technical nature as related to quantitative measurement and proper control of the method

Definition of the limits of quantitative significance of data From the above discussion, it is apparent that a qualitative determination may have significance in diagnosis within wide limits of variation of the data The very observation that blood is present in vomitus is a *qualitative datum* that determines the *presence or absence* of a substance The crude observation that the vomitus contains a large, moderate or small amount of blood is a *semiquantitative datum* that has value even though the absolute number of milligrams of hemoglobin in the sample can be given only within wide limits In a quantitative determination, it is necessary to define the significance of the final result if it is to be interpreted properly This is most readily done by one of several statistical methods The physician

*Two coefficients of variation

†Two coefficients of variation

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35391

PRESENTATION OF CASE

A forty-two-year-old handy man was admitted to the hospital because of anorexia and diarrhea.

The patient had been well until eleven years before entry, when he noted progressive enlargement of the lymph nodes of the neck. He was admitted to another hospital where a biopsy of one of the lymph nodes was performed and a subsequent diagnosis of Hodgkin's lymphoma rendered. He received several courses of x-ray therapy for recurrent masses in the neck with good results and was well until two years before the present admission when he was admitted to this hospital because of anorexia, vomiting, nausea and weight loss of 36 pounds of five months' duration.

Physical examination revealed a generalized superficial lymphadenopathy and a moderately enlarged spleen. A repeat biopsy of the axillary lymph nodes confirmed the previous diagnosis of Hodgkin's lymphoma. The patient was considered a "terminal problem" and was given six doses of nitrogen mustard following which he made a striking recovery, became asymptomatic, regained his normal weight and was soon back at work. Eight months later, however, because of recurrent symptoms and weight loss, he was readmitted and given five doses of nitrogen mustard following which he again responded dramatically with subsequent return to work. Four months before the present admission he was seen in the Tumor Clinic, where he complained of another recurrence of symptoms and at which time palpable inguinal lymph nodes were found. The patient was given x-ray therapy with diminution in the size of the masses in these areas. Six weeks before admission he returned to the Tumor Clinic, still complaining of nausea, weakness and weight loss. At this time physical examination failed to show any lymphadenopathy. One week prior to entry he complained of diarrhea of one

month's duration. Stools occurred six to nine times daily, were watery brown without mucus or blood and were accompanied by severe cramps and tenesmus. There had been a 20-pound weight loss but no vomiting and only slight nausea. General malaise and weakness had been progressive.

Examination showed an emaciated, somewhat pale middle-aged man in no acute distress. There was slight to moderate generalized lymphadenopathy. The heart was not enlarged, the rhythm was regular, and the aortic second sound was greater than the pulmonic. A Grade I systolic murmur was present at the apex. The abdomen was normal except for considerable voluntary spasm. There was ++ pitting edema of the ankles.

The blood pressure was 100 systolic, 65 diastolic. The temperature, pulse and respirations were normal.

The urine was yellowish brown and gave a ++++ test for albumin. The sediment contained rare red cells and 5 to 10 white cells per high-power field and many granular casts. Examination of the blood disclosed a red-cell count of 3,300,000, with a hemoglobin of 13.3 gm, and a white-cell count of 11,100, with 89 per cent neutrophils. A smear showed a normocytic, normochromic anemia. A stool was guaiac negative.

Because of the patient's previous good response to nitrogen mustard therapy it was decided to treat him again in this way, and he was subsequently given five doses of 65 mg of nitrogen mustard intravenously over a five-day period. After two days in the hospital, apparently in response to antispasmodic treatment, diarrhea decreased to one or two watery movements a day. The appetite remained poor, however, and symptomatically there was little change. A roentgenogram of the chest showed clear lung fields and no definite hilar-lymph-node enlargement. A barium enema was negative. Agglutination tests for brucella and organisms of the typhoid-para-typhoid group were negative.

On the fifth hospital day some presacral edema was noted, and there was a suggestion of a small amount of ascites.

On the sixth hospital day laboratory examination showed a serum protein of 3.54 gm per 100 cc, with an albumin of 1.79 gm, and a globulin of 1.75 gm per 100 cc. (albumin-globulin ratio of 1). The nonprotein nitrogen was 62 mg per 100 cc, the sodium 126.5 milliequiv per liter, the carbon dioxide 28 milliequiv per liter, the prothrombin time 29 (normal 15 seconds), calcium 5.3 mg per 100 cc, phosphorus 7.3 mg per 100 cc, and phosphatase 61 units per 100 cc. A Congo-red test showed a small amount of dye in the five-minute specimen and almost none in the sixty-minute specimen. On the same day, during an attempted gastrointestinal series, the patient became very weak and upon return to the ward was found to be in shock, with a blood pressure of 60 systolic, 0

numerical limits $M \pm 2\sigma$ —that is, between two standard deviations above and below the mean. The chance that a single observation will fall within these limits is therefore 95 in 100, the chance that it will fall outside these limits is 5 in 100. An observation falling outside these limits is thus considered abnormal, although the chance is 0.05 that it is not.

Numerical Expression of the Degree of Variation of Data, Calculation of the Coefficient of Variation

As the definition of σ shows, the limits of variation are always expressed in the same units as the

TABLE 7 Example of the Calculation of the Standard Deviation σ from Eleven Determinations of the Red-Cell Count

RED CELL COUNT, λ	DEVIATION FROM MEAN $d [=(X-M)]$	d^2
millions/mm ³	millions/mm ³	
3.6	+0.1	0.01
3.7	+0.2	0.04
3.2	-0.3	0.09
3.5	0.0	0.00
3.6	+0.1	0.01
3.2	-0.3	0.09
3.5	0.0	0.00
3.4	-0.1	0.01
3.6	+0.1	0.01
3.5	0.0	0.00
3.5	0.0	0.00
$\Sigma \lambda = 38.3$		$\Sigma d^2 = 0.26$

$$N = 11$$

$$M = \frac{\Sigma X}{N} = \frac{38.3}{11} = 3.5$$

$$\sigma = \sqrt{\frac{\Sigma d^2}{N-1}} = \sqrt{\frac{0.26}{10}} = \sqrt{0.026} = \pm 0.16 \text{ million/mm}^3$$

quantity measured, thus, for the red-cell count, the units are millions per cubic millimeter, for hemoglobin, grams per 100 ml, and for the hematocrit, per cent. The standard deviations of determinations of red-cell count, hemoglobin and hematocrit cannot be directly compared with one another because the units differ. However, comparison can be made between quantities that have no units. For this purpose there is the *coefficient of variation*, C V, which is defined as the ratio of the standard deviation to the mean, and may be expressed in per cent. Thus, $C V = (\sigma/M) \times 100$ per cent.

From the example in Table 7, where $\sigma = \pm 0.16$ million red cells/mm³, it is found that

$$C V = \frac{\pm 0.16}{3.5} \times 100 = \pm 4.6 \text{ per cent}$$

The interpretation of two coefficients of variation (2 C V) is the same as that of two standard deviations (2 σ), the only difference being the units of expression.

SUMMARY AND RECOMMENDATIONS

The physician himself will recognize the limits of significance of qualitative and semiquantitative determinations. However, he may have no way of knowing and, therefore, *must be informed* of the limits of significance of data obtained by a quantitative determination. Thus, it might be within practical possibility to record clinical data with a statement of the limits of significance, as indicated for certain tests in Table 6, for example, calcium, 10 mg/100 ml (2 C V \pm 5 per cent), red-cell count, 1.8 10^6 /mm³ (2 C V \pm 14 per cent), hemoglobin 12 gm/100 ml (2 C V \pm 15 per cent), total protein, 6.2 gm/100 ml serum (2 C V \pm 10 per cent). An individual laboratory worker can control subjective errors, and can determine and state precisely the objective error of any given method, with much benefit to the accuracy and significance of expensive and important laboratory results.

I am indebted to Mr. Joseph D. Elder, of the Harvard University Press, for contributions on the units of measure, and to Miss Jane Worcester, of the Harvard School of Public Health, and to Dr. Fred H. Allen, of the Children's Hospital, for aiding in the section on quantitative evaluation of data.

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In summary, I believe the patient had Hodgkin's disease that involved the intestine, with perforation and peritonitis, and that he had secondary amyloidosis with the chief clinical manifestation of amyloid nephritis with uremia

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DR SHORT They were considered normal in the protocol That is why I did not ask for them

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CLINICAL DIAGNOSES

Hodgkin's disease.

Uremia

Amyloidosis?

DR SHORT'S DIAGNOSES

Hodgkin's disease, involving intestine, with perforation and peritonitis

Secondary amyloidosis, chiefly involving kidneys

ANATOMICAL DIAGNOSES

Malignant lymphoma, Hodgkin's type, involving lymph nodes only

Amyloidosis of liver, adrenal glands and especially of kidneys and lymph nodes

Amyloid nephrosis (with uremia)

Acute enteritis

PATHOLOGICAL DISCUSSION

DR CASTLEMAN A review of the biopsy of the lymph node removed two years previously showed Hodgkin's disease, of the type that has been described by Jackson and Parker¹ as very early—what they call Hodgkin's paraganuloma In this type the architecture of the nodes is not too markedly distorted, there is no evidence of fibrosis and only a few eosinophils, but the Reed-Sternberg cells are present This microscopical picture would fit in with the long history of Hodgkin's disease that this patient had—thirteen years Jackson and Parker¹ have reported cases in which patients with nodes of this character have lived for as long as twenty-five years and in which the nodes retain their paraganuloma appearance without ever going over into a true Hodgkin's granuloma or the more classic Hodgkin's disease

Autopsy showed large numbers of nodes in the mediastinum and retroperitoneal areas predominantly, as well as in the cervical and axillary regions Some of them were quite large, especially in the abdomen, along the aorta, forming masses reaching 9 cm in length When these were cut, they were quite firm and almost fibrous Grossly it was believed to be Hodgkin's disease Microscopical examination, however, showed that it was practically all amyloid One has to hunt to find any cell that could be called a Reed-Sternberg cell of Hodgkin's disease We sectioned about 20 nodes, and all showed the same picture diffuse replacement by amyloid, with a periphery of cells and an occasional Sternberg cell Going back to the original node removed two years before the final admission, we found no evidence of amyloid, so that we have evidence, I believe, that the amyloid developed within a two-year period Since every node examined at autopsy was involved with amyloid, it would be a little farfetched to think that this particular biopsied node escaped at that time We found no evidence of Hodgkin's disease in the liver, spleen, kidney or intestines There was amyloid disease in the liver, kidney, and adrenal glands, but in no other organ, except the nodes

The kidneys were very big, weighing 800 gm together, which is about two and a half times the

diastolic The pulse was 120 Physical examination at this time did not reveal a cause for the change in the patient's condition, but peristalsis was noted to be absent A roentgenogram of the abdomen was negative for free air Following a transfusion of 1000 cc of blood the blood pressure rose to 98 systolic, 58 diastolic Despite this improvement the patient was still irrational at times The skin was warm and moist, the lungs clear, and the heart rate 98 and regular The abdomen was moderately distended, soft and diffusely tender but without rebound tenderness Peristalsis was absent There was no vomiting On the seventh hospital day the patient appeared toxic but was not in the profound shock of the previous day Early in the day the physical findings were unchanged, but later peristalsis was heard A stool gave a ++ guaiac reaction, and the blood hemoglobin was 11.5 gm Five hundred cubic centimeters of brown, watery fluid was aspirated from the stomach and gave a + guaiac reaction Despite additional blood and supportive therapy the patient's course was progressively downhill On the eighth hospital day he was incontinent and passed foul, yellowish-gray fluid material by rectum Oral fluid intake was limited because of nausea, and intravenous fluid intake was intentionally kept somewhat low in the face of the ankle edema and ascites The systolic blood pressure was 166 The nonprotein nitrogen remained low, and urine output was depressed On the ninth hospital day he was found dead in bed

Whereas urine examinations previous to this admission had been negative, six different examinations during this period of hospitalization gave ++++ tests for albumin, and the sediment contained 4 to 6 white cells and red cells per high-power field All specimens contained numerous hyaline and granular casts The specific gravity ranged from 1.012 to 1.015 The white-cell count, which had been 11,100 on admission, fell progressively to a low of 2200 on the seventh hospital day

DIFFERENTIAL DIAGNOSIS

DR CHARLES L. SHORT The original diagnosis of Hodgkin's disease in this patient was made by biopsy eleven years before his final admission He had an unusually long remission, nine years, following the first course of x-ray therapy It would be of interest to learn from the pathologist whether the original biopsy showed a less malignant type, according to Jackson and Parker's¹ classification, than the second one taken two years before his death The patient was next treated with nitrogen mustard and twice made striking responses, with remissions lasting eight and ten months respectively This case demonstrates the value, at times, of nitrogen mustard treatment

Six weeks before his final admission, a new train of symptoms appeared that seemed to be localized to the gastrointestinal tract in the form of intrac-

table diarrhea The finding of generalized adenopathy on admission points to a recurrence of Hodgkin's disease, but the urinary findings can hardly be explained on that basis The patient's course was rapidly downhill, with the development of edema and ascites and finally uremia The episode on the sixth hospital day suggests intestinal perforation, with peritonitis, probably localized, or the point of perforation sealed off fairly rapidly, since peristalsis reappeared and there were never any frank signs of generalized peritonitis The final discharge of foul fluid from the rectum may have represented perforation and drainage of an abscess by this route

The next question to be decided is whether the patient died of Hodgkin's disease or a complication of this condition, or whether the treatment employed had anything to do with it Perhaps a combination of these three factors was active I think the diagnosis of amyloidosis secondary to Hodgkin's disease can be made with reasonable certainty in this patient in view of the nearly complete disappearance of Congo red from the blood stream A recent paper from the Mayo Clinic² states that in 2 cases out of 30 of secondary amyloidosis the primary lesion was Hodgkin's disease

The blood chemical findings revealed an elevated nonprotein nitrogen, a low serum protein and altered serum calcium and phosphorus values I do not believe it is necessary to bring in the possibility of parathyroid destruction by amyloid or tumor to explain these calcium and phosphorus values In fact, I do not know of any such cases as yet reported Low serum sodium and hypotension suggest Addison's disease, which rarely occurs secondary to amyloidosis or to neoplasm I think there is no way of making the diagnosis without further evidence, although amyloid deposits were probably found in the adrenal cortex at autopsy This is a common site for secondary amyloidosis Deposits were also probably found in the liver but not to the extent of producing any severe dysfunction of this organ The increased prothrombin time may be accounted for by malabsorption due to the intestinal disease

We are left with the diarrhea and probable intestinal perforation to explain Although the small intestine may be involved in amyloidosis to the extent of diarrhea and even a sprue-like syndrome, I have been unable to find any cases going on to actual perforation Nitrogen mustard in at least 2 cases³ has apparently produced ulceration and perforation of the gastrointestinal tract, but this complication must be rare Furthermore, this patient's diarrhea had started before the last administration of the nitrogen mustard Involvement of the intestine is not uncommon in Hodgkin's disease and may lead to ulceration and perforation I would prefer this explanation for the abdominal findings, with the possibility that the perforation was due to destruction of Hodgkin's tissue by the nitrogen mustard

In summary, I believe the patient had Hodgkin's disease that involved the intestine, with perforation and peritonitis, and that he had secondary amyloidosis with the chief clinical manifestation of amyloid nephritis with uremia

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DR CASTLEMAN A review of the biopsy of the lymph node removed two years previously showed Hodgkin's disease, of the type that has been described by Jackson and Parker¹ as very early—what they call Hodgkin's paragranuloma In this type the architecture of the nodes is not too markedly distorted, there is no evidence of fibrosis and only a few eosinophils, but the Reed-Sternberg cells are present This microscopical picture would fit in with the long history of Hodgkin's disease that this patient had—thirteen years Jackson and Parker¹ have reported cases in which patients with nodes of this character have lived for as long as twenty-five years and in which the nodes retain their paragranuloma appearance without ever going over into a true Hodgkin's granuloma or the more classic Hodgkin's disease

Autopsy showed large numbers of nodes in the mediastinum and retroperitoneal areas predominantly, as well as in the cervical and axillary regions Some of them were quite large, especially in the abdomen, along the aorta, forming masses reaching 9 cm in length When these were cut, they were quite firm and almost fibrous Grossly it was believed to be Hodgkin's disease Microscopical examination, however, showed that it was practically all amyloid One has to hunt to find any cell that could be called a Reed-Sternberg cell of Hodgkin's disease We sectioned about 20 nodes, and all showed the same picture diffuse replacement by amyloid, with a periphery of cells and an occasional Sternberg cell Going back to the original node removed two years before the final admission, we found no evidence of amyloid, so that we have evidence, I believe, that the amyloid developed within a two-year period Since every node examined at autopsy was involved with amyloid, it would be a little farfetched to think that this particular biopsied node escaped at that time We found no evidence of Hodgkin's disease in the liver, spleen, kidney or intestines There was amyloid disease in the liver, kidney, and adrenal glands, but in no other organ, except the nodes

The kidneys were very big, weighing 800 gm together, which is about two and a half times the

normal weight, and they were very pale and glassy. There was very little evidence of scarring. Practically every glomerulus was involved with amyloid, but rarely was a whole corpuscle completely replaced. The striking finding in this case was in the tubules, which were plugged with casts, and the epithelial cells were swollen and filled with hyaline granules — characteristic of so-called amyloid nephrosis. The intestines, both colon and small bowel, showed scattered areas of hemorrhage, and on microscopical examination there was some cellular infiltration of the submucosa, an acute or subacute process, similar to what we have seen occasionally in uremia. There were, however, no ulcerations in the bowel. Whether this was due to the uremia or uremia in addition to the effect of nitrogen mustard, I do not know. I cannot account for the intestinal obstruction satisfactorily unless it was paralytic ileus as a result of uremia.

DR WYMAN: I was thinking in terms of ileus as a result of vascular accident or uremia possibly to account for the picture.

DR CASTLEMAN: The association of amyloidosis with Hodgkin's disease is not very common. Dr Morgan, of our resident staff, looked up our cases and found that of 60 cases of Hodgkin's disease 5 had amyloidosis. It is interesting that in the series at the Boston City Hospital, reported by Jackson and Parker,¹ there was 1 case very similar to this one in which the amyloid was limited to lymph nodes, replacing them almost completely.

DR JAMES H. CURRENS: Ileus has been described with potassium deficiency.⁵ We have no information here, but it would be interesting to know whether he was losing excess potassium or retaining potassium. Occasionally, these patients, particularly with vomiting, can lose tremendous amounts of potassium, which may result in ileus.

DR CASTLEMAN: What about the level of potassium in uremia?

DR CURRENS: It may be high or low, it is usually high, but occasionally it may be low. Recently, a patient died in this hospital with a nonprotein nitrogen of 150 mg per 100 cc, and a serum potassium of 12 milliequiv per liter (normal, 3.5 to 5.0 milliequiv per liter). It is a possible explanation.

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CASE 35392

PRESENTATION OF CASE

First admission. A thirty-nine-year-old housewife entered the hospital complaining of swollen legs.

At the age of fourteen the patient had severe pains in the feet and ankles. A heart murmur was noted, and she was kept in bed for about six months. With clearing of the joint pains she was allowed to resume normal activities but on doing so developed "Saint Vitus dance," described as purposeless twitchings of the hands and arms, which lasted about one and a half years, and then disappeared completely. The patient was well until the age of twenty-four, when, two weeks before the birth of her first child, she developed ankle edema that cleared spontaneously after delivery. She was then free of symptoms until one year prior to admission, when she developed palpitations and exertional dyspnea. Shortly before entry she noted ankle swelling, severe exertional dyspnea and orthopnea requiring three pillows, with almost weekly attacks of paroxysmal nocturnal dyspnea. There was no cough, chest pain, or fever.

Physical examination revealed marked engorgement and pulsation of the neck veins. Many moist rales were present throughout both lung fields. The heart rate was rapid and irregular, with an apical rate of 110 and a radial pulse of 96. There were enlargement of the heart to percussion and an apical systolic thrill. Harsh apical systolic and diastolic murmurs and a blowing diastolic murmur in the aortic area were heard. The liver edge was 5 cm below the costal margin. The ankles and calves showed marked pitting edema.

The temperature was 99.2°F, and the respirations were 24. The blood pressure was 174 systolic, 98 diastolic.

Laboratory studies on the urine showed a specific gravity of 1.018, with a trace of albumin. Blood studies, including the white-cell count, nonprotein nitrogen, carbon dioxide and total protein, were not remarkable. An electrocardiogram demonstrated auricular fibrillation alternating with idioventricular rhythm. X-ray studies of the chest showed a small amount of fluid in the left costophrenic angle and considerable generalized cardiac enlargement.

Following digitalization the patient improved steadily until two and a half weeks had elapsed, and then she suddenly developed severe pain in the right lower chest and hemoptysis. Roentgenograms revealed a large area and several smaller areas of increased density in the right lower lobe. Surgical interruption of both common femoral veins was done, but no clots were found. Improvement was slow but steady, and after three months the patient returned home on a regimen of digitalis, ammonium chloride and weekly injections of mercurhydrin.

Second admission (four months later). The patient did well until approximately four months

after the first admission, when she again developed severe pain in the lower chest for which she was readmitted. Chest x-ray films showed a new area of increased density in the anterior portion of the right lower lobe. Heparin and dicumarol were instituted, and shortly thereafter she became asymptomatic and was discharged two weeks later.

Final admission (one year later) Over the ensuing year the patient enjoyed limited activity and was fairly well until two weeks prior to re-entry. Rather suddenly she became extremely nervous and jittery and developed coarse, involuntary tremor of the hands and feet. She had several, apparently unprovoked, episodes of uncontrollable shrieking and crying and other sudden episodes of confusion, disorientation and memory disturbances. With the onset of these symptoms she noted a diffuse, slightly itchy erythema of the hands, feet and extensor surfaces of the forearms and lower legs. There was no fever, chills, chest pain or hemoptysis, and no evidence of embolic phenomena.

On physical examination the patient lay in bed in no acute discomfort, but there were occasional twitchings of the hands and feet. There was a diffuse, rose-red erythema over the dorsal surfaces of the hands and feet and the extensor surfaces of the legs and forearms, which blanched on pressure. The skin was cool and moist. The neck veins were engorged and pulsating. The lungs were clear except for an area of dullness at the right posterior base. The heart showed no change from previous examinations. The remainder of the examination, including the neurologic examination, was negative except for moderate pitting edema of the ankles.

The temperature was 97°F, the pulse 88, and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

Examination of the blood revealed a white-cell count of 12,000, with 66 per cent neutrophils, 25 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. An electrocardiogram showed a rate of 90. The QRS complex was 0.07, and the T waves were obscured by coarse auricular fibrillations. There was right-axis deviation. Chest x-ray films showed linear scarring in the region of the previous densities in the lung fields and little change in the heart. The sodium was 139.5 milliequiv, and the chloride 102 milliequiv per liter and the nonprotein nitrogen 66 mg per 100 cc.

The erythema had disappeared, and the coarse tremors of the extremities had diminished by the day after admission. Over the next two days, however, the patient's behavior became more bizarre, with almost continuous hysterical crying and thrashing about the bed. Much of the time she seemed entirely out of contact with her surroundings. Despite the marked behavior change, examination showed only cyanosis of the extremities and a dusky, reddish-purple discoloration of the skin.

Her condition rapidly deteriorated, and by the sixth hospital day she was completely unresponsive. The cyanosis had gradually deepened, and she became markedly dyspneic and hyperpneic. The apical pulse was 112, and the radial pulse 52. However, the lungs remained clear. Despite oxygen therapy the cyanosis progressively deepened, and the pulse gradually weakened. The temperature spiked to 105°F, the circulation slowly failed, and she died on the seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR GORDON S MYER This patient seemed to present no unusual problem until the time of her third and final admission to the hospital. There is a history perfectly consistent with the occurrence of active rheumatic fever and chorea at the age of fourteen, at which time a heart murmur was noted. The onset of rheumatic fever as late in childhood as this and the associated chorea would both favor a relatively good prognosis. This was borne out since she was apparently quite well until the age of thirty-six or thirty-seven years except for one brief episode of ankle edema, which may or may not have represented mild congestive failure toward the end of her pregnancy at twenty-four years of age.

One year prior to her first admission to the hospital the patient went into definite congestive heart failure associated with palpitation, which evidently represented the onset of auricular fibrillation. Such an association between the occurrence of auricular fibrillation and the appearance of heart failure is certainly common in patients with rheumatic heart disease. Physical examination indicated the presence of pulmonary congestion and right-sided failure on the basis of rheumatic heart disease with mitral stenosis and regurgitation and aortic regurgitation and auricular fibrillation and with a rather rapid ventricular rate and a pulse deficit. In addition, a slight hypertension was present and there was some albuminuria. The appearance of a small amount of fluid in the left pleural cavity makes one think of pulmonary embolus even then, since in uncomplicated heart failure the right pleural cavity is most apt to accumulate fluid first. In any case, she later evidenced the classic signs and symptoms of pulmonary emboli, for which femoral-vein ligation was carried out. She was then sent out on routine therapy for control of the congestive failure.

The second admission to the hospital was occasioned by the recurrence of chest pain. When chest x-ray films revealed changes consistent with a new pulmonary infarct she was given anticoagulant therapy. Where did the embolus arise? It may, of course, have come from the common femoral arteries above the point of their ligation or from veins in the pelvis, but a more likely source would be a thrombus in the right auricle.

We now come to what I believe is the central problem. What was the nature of the complication

normal weight, and they were very pale and glassy. There was very little evidence of scarring. Practically every glomerulus was involved with amyloid, but rarely was a whole corpuscle completely replaced. The striking finding in this case was in the tubules, which were plugged with casts, and the epithelial cells were swollen and filled with hyaline granules — characteristic of so-called amyloid nephrosis. The intestines, both colon and small bowel, showed scattered areas of hemorrhage, and on microscopical examination there was some cellular infiltration of the submucosa, an acute or subacute process, similar to what we have seen occasionally in uremia. There were, however, no ulcerations in the bowel. Whether this was due to the uremia or uremia in addition to the effect of nitrogen mustard, I do not know. I cannot account for the intestinal obstruction satisfactorily unless it was paralytic ileus as a result of uremia.

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Second admission (four months later). The patient did well until approximately four months

In conclusion, I believe this patient had rheumatic heart disease, with mitral stenosis and regurgitation, aortic regurgitation and auricular fibrillation. Evidence of active rheumatic fever may have been found. Congestive heart failure was certainly present. In addition, I would postulate recurrent pulmonary emboli, perhaps arising from the right auricle, with terminal pulmonary embolization or thrombosis within the pulmonary arterial tree and cor pulmonale leading to death. I think the azotemia and albuminuria were more likely due to congestive failure than to complicating intrinsic renal disease. A "toxic" psychosis, with perhaps some element of lithium intoxication, seems the best explanation of the episodes of confusion and delirium so prominent at the time of her terminal illness.

CLINICAL DIAGNOSES

Rheumatic heart disease with mitral stenosis
Auricular fibrillation
Progressive cerebral thrombosis

DR MYERS'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis
and regurgitation, aortic regurgitation and
auricular fibrillation
Active rheumatic fever?
Pulmonary embolism, from right-auricle thrombi,
with cor pulmonale
Toxic psychosis from lithium intoxication?

ANATOMICAL DIAGNOSES

Pulmonary embolism, massive, acute
Mural thrombi, both auricles
Endocarditis chronic active rheumatic, mitral
and aortic, with mitral stenosis
Healed pulmonary infarcts
Congestion of lung, liver and spleen
Cerebral emboli, microscopic
Cardiac hypertrophy right.
Renal infarct

PATHOLOGICAL DISCUSSION

DR CASTLEMAN Post-mortem examination showed an enlarged heart, weighing 430 gm. There was marked dilatation of both auricles and dilatation and hypertrophy of the right ventricle, which was about twice normal in thickness — findings characteristic of the mitral heart. This was confirmed when the heart was opened, the mitral orifice barely admitting the tip of the little finger. Although the aortic cusps were thickened and in places calcified, there was no evidence of interadherence to produce any stenosis. Microscopically, above the margins of both valves there was active fibroblastic proliferation consistent with chronic active rheumatic infection. Although I could find no Aschoff nodules in the myocardium, I believe the cellular proliferation in the valves indicates a process that was still in a healing stage.

As evidence of the auricular fibrillation we found mural thrombi in both auricular appendages, and these probably were the source of the emboli to the lungs from the right auricle and to the kidney and brain from the left. There were both old and recent emboli within the pulmonary circuit, the recent ones being in the main vessels and the immediate cause of death, the older ones were in the smaller vessels and in relation to healed infarcts.

In several microscopical sections of the cerebrum, there were many small arteries occluded by old recanalized thrombi as well as more recent occlusions, unquestionably representing emboli. There were a few small foci of infarction. There was no evidence of an endarteritis, and I believe that many of the cases of so-called rheumatic endarteritis are probably on an embolic basis. There were no changes to suggest a toxic process.

that led to the patient's death? Since the onset of her terminal illness was characterized by tremors and disorientation and the appearance of a pruritic dermatitis, one immediately wonders about medication. May we know what drugs she had been receiving between the second and third admissions? Had she been taking lithium chloride as a salt substitute?

DR BENJAMIN CASTLEMAN She had been followed in the Out-Patient Department and given digitalis, ammonium chloride and mercurial injections. In addition she had been put on a low-sodium diet and had been given a lithium chloride preparation starting about a month before her final admission to the hospital.

DR MYERS Do we know how much lithium chloride the patient actually consumed? Also, did she continue to receive the salt substitute after admission?

DR CASTLEMAN There is no record of the actual amount ingested. She did continue to receive the salt substitute ad lib after admission to the hospital.

DR MYERS It would be possible to explain this patient's coarse tremors and disorientation on the basis of lithium intoxication. She apparently was taking it for only a short time prior to the onset of her acute symptoms, but she may have taken far more than was recommended, as some patients do. Also we learn that her renal status was unsatisfactory, with a nonprotein nitrogen of 66 mg per 100 cc, so that the excretion of lithium may have been unusually poor. As far as I know lithium poisoning has not been associated with the appearance of a skin rash, however. Neurologic manifestations of digitalis toxicity, including restlessness, disorientation, delirium and tremors, in the absence of other evidence of digitalis poisoning have been reported, but these are certainly very rare and again would not account for the pruritic erythema of the skin. She had apparently not ingested bromides, barbiturates or salicylates. It seems highly unlikely that the mercurial injections can be implicated. Patients on the low-sodium diet may occasionally become weak, confused or comatose, with a high nonprotein nitrogen and low serum sodium level, but that was not the picture here. Although mental aberrations on the basis of cortical-vessel involvement in rheumatic fever have been considered to occur, the evidence for this is unsatisfactory, and the associated erythema as described

is not like that of the rheumatic erythemas ordinarily encountered. The neurologic examination was negative, and the evidence does not favor the occurrence of multiple cerebral emboli from the left auricle or from a focus of bacterial endocarditis on the mitral or aortic valves. I am forced to the conclusion that this patient had a "toxic" psychosis in association with congestive heart failure, cerebral anoxia and azotemia. Lithium intoxication may also have played a role. I cannot satisfactorily explain the skin rash, and that is disturbing.

We are still left with the problem of the final cause of death.

At the time of her final admission the patient exhibited signs of right-sided cardiac failure without evident pulmonary congestion. The heart murmurs were unchanged, and the auricular fibrillation was moderately well controlled as to ventricular rate. There was no elevation of temperature or marked leukocytosis, and the chest x-ray film failed to reveal fresh pulmonary infarcts. The appearance of right-axis deviation in the electrocardiogram, not mentioned as having been present at the time of the first admission, may have been on the basis of mitral stenosis and due to right ventricular strain resulting from repeated pulmonary emboli as well. The elevated nonprotein nitrogen may merely represent prerenal azotemia on the basis of congestive heart failure. What did urinalysis show at the time of the last admission?

DR CASTLEMAN The specific gravity was 1.012, with a +++ test for albumin and the sediment showed 15 to 20 epithelial cells per high-power field and a few white cells but no red cells.

DR MYERS Heart failure could also account for the presence of albuminuria. We seem to have no evidence, other than the rather low specific gravity, to suggest complicating renal disease.

The last few days in the hospital were marked by a rapid downhill course, with delirium followed by coma. She became progressively more cyanotic and dyspneic, tachycardia became more marked, and a sharp temperature elevation occurred just before death. Despite marked respiratory distress the lungs were clear. I believe that terminal pulmonary embolism or thrombosis in the pulmonary arterial tree may explain this picture. In such a case actual new pulmonary infarcts may or may not have occurred. Active rheumatism cannot be ruled out.

In conclusion, I believe this patient had rheumatic heart disease, with mitral stenosis and regurgitation, aortic regurgitation and auricular fibrillation. Evidence of active rheumatic fever may have been found. Congestive heart failure was certainly present. In addition, I would postulate recurrent pulmonary emboli, perhaps arising from the right auricle, with terminal pulmonary embolization or thrombosis within the pulmonary arterial tree and cor pulmonale leading to death. I think the azotemia and albuminuria were more likely due to congestive failure than to complicating intrinsic renal disease. A "toxic" psychosis, with perhaps some element of lithium intoxication, seems the best explanation of the episodes of confusion and delirium so prominent at the time of her terminal illness.

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SIGNERS OF THE PROTEST

THE signers of the Protest of January 31, 1949, to the American Medical Association have continued since that time to lead a loosely corporate existence. Their original protest was against the levying of the famous twenty-five dollar assessment unless or until some adequate guarantee could be given that the policies and methods of the Association in combating compulsory health insurance would be more constructive and progressive than previous indications had led one to expect.

The same unhappy flair for infelicitous publicity that characterized the actions of the House of Delegates in adopting the assessment and, at a subsequent meeting, in repudiating the Association's editor greeted the protest. As a result a number of physicians who had only the welfare of their profession at heart came under the suspicion of having betrayed organized medicine instead

of guarding its honor with more than ordinary zeal.

Since that time a number of the signers of the protest have paid the assessment—some, no doubt, because they acknowledged the legality of the levy, regardless of its purpose, others because of a reasonable assurance that the Association was really embarked on a constructive campaign for the equitable distribution of medical service. The announcement of a national representative health assembly to be held this fall gave promise also that the Association's twelve-point program, existing at present only as a statement of impeccable principles, might in reality become a program, devoted to action.

The signers of the protest have continued to interest themselves in health legislation, and have shown a commendable desire to keep informed on the subject. Most recent interest in this respect has had to do with the Flanders-Ives Bill (S 1970) and its identical companion House bills (4918 through 4924), introduced by Messrs Herter, Javits, Case, Nixon, Morton, Fulton and Hale. The opinion of the "signers" has been sought on this prospective legislation in the light of a statement made by Dr. George Baehr on behalf of the New York Academy of Medicine, at the public hearings before the Senate Committee on Education and Labor, on June 20, 1949.

The Academy, which, in 1946 and 1947, urged enactment of legislation "to provide federal grants-in-aid to the states for the study of state and local needs and the development of state and local programs designed to correct those deficiencies in accordance with acceptable federal standards," is not interested in maintaining the status quo. It is, on the contrary, "prepared to consider any change in the methods of rendering medical services and of payment for medical care which may be better for the people."

S 1970, according to Dr. Baehr, comes most nearly, of all the bills under consideration, to meeting all the Academy's requirements for a voluntary prepaid comprehensive medical-service plan. Two excellent features of the bill are the provisions for the gradual development of its program, with the encouragement of medical groups,

and the creation of a bipartisan federal health study and planning commission to make a survey of health service needs and report to Congress in 1953

The fears of the Subcommittee on National Legislation of the Massachusetts Medical Society, as expressed last May to Congressman Herter, are that this bill, if passed, would ultimately result in the absorption by the federal Government of voluntary, nonprofit, prepayment medical and hospital-care plans. No mention is made in it of employer contributions, nor is the method of financing clearly defined. Ostensibly subscribers would pay in accordance with their ability to pay, the chief financial burden being carried by those with greater-than-average incomes, who would pay in much more than they would take out.

What is obviously needed more than anything else, if the best health plan possible is to be devised for the nation, is a meeting of the most capable minds, without heat and without acrimony.

FOOD FOR THOUGHT

THE latest program undertaken by "CARE"—Cooperative for American Remittances to Europe, Inc.—is to provide food for the hungry intellects of Europe. Reduced indeed is the pabulum that nourishes the mind, for at no time in the history of the world have so many books been destroyed as in the past decade.

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SIGNERS OF THE PROTEST

THE signers of the Protest of January 31, 1949, to the American Medical Association have continued since that time to lead a loosely corporate existence. Their original protest was against the levying of the famous twenty-five dollar assessment unless or until some adequate guarantee could be given that the policies and methods of the Association in combating compulsory health insurance would be more constructive and progressive than previous indications had led one to expect.

The same unhappy flair for infelicitous publicity that characterized the actions of the House of Delegates in adopting the assessment and, at a subsequent meeting, in repudiating the Association's editor greeted the protest. As a result a number of physicians who had only the welfare of their profession at heart came under the suspicion of having betrayed organized medicine instead

of guarding its honor with more than ordinary zeal.

Since that time a number of the signers of the protest have paid the assessment—some, no doubt, because they acknowledged the legality of the levy, regardless of its purpose, others because of a reasonable assurance that the Association was really embarked on a constructive campaign for the equitable distribution of medical service. The announcement of a national representative health assembly to be held this fall gave promise also that the Association's twelve-point program, existing at present only as a statement of impeccable principles, might in reality become a program, devoted to action.

The signers of the protest have continued to interest themselves in health legislation, and have shown a commendable desire to keep informed on the subject. Most recent interest in this respect has had to do with the Flanders-Ives Bill (S 1970) and its identical companion House bills (4918 through 4924), introduced by Messrs Herter, Javits, Case, Nixon, Morton, Fulton and Hale. The opinion of the "signers" has been sought on this prospective legislation in the light of a statement made by Dr. George Baehr on behalf of the New York Academy of Medicine, at the public hearings before the Senate Committee on Education and Labor, on June 20, 1949.

The Academy, which, in 1946 and 1947, urged enactment of legislation "to provide federal grants-in-aid to the states for the study of state and local needs and the development of state and local programs designed to correct those deficiencies in accordance with acceptable federal standards," is not interested in maintaining the status quo. It is, on the contrary, "prepared to consider any change in the methods of rendering medical services and of payment for medical care which may be better for the people."

S 1970, according to Dr. Baehr, comes most nearly, of all the bills under consideration, to meeting all the Academy's requirements for a voluntary prepaid comprehensive medical-service plan. Two excellent features of the bill are the provisions for the gradual development of its program, with the encouragement of medical groups,

and the creation of a bipartisan federal health study and planning commission to make a survey of health service needs and report to Congress in 1953

The fears of the Subcommittee on National Legislation of the Massachusetts Medical Society, as expressed last May to Congressman Herter, are that this bill, if passed, would ultimately result in the absorption by the federal Government of voluntary, nonprofit, prepayment medical and hospital-care plans. No mention is made in it of employer contributions, nor is the method of financing clearly defined. Ostensibly subscribers would pay in accordance with their ability to pay, the chief financial burden being carried by those with greater-than-average incomes, who would pay in much more than they would take out.

What is obviously needed more than anything else, if the best health plan possible is to be devised for the nation, is a meeting of the most capable minds, without heat and without acrimony.

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The important agent, however, must be the physician, who has available the necessary follow-up technic and who will find in this occasion an op-

portunity to demonstrate publicly that his real concern in the practice of medicine is that of service rather than reward. This is a lesson to be impressed upon a somewhat skeptical public that is inclined to find actions more eloquent than words.

PRIZE-ESSAY COMPETITION

THE *Journal* announces that a prize-essay contest will be open to all members of the class of 1950 registered in any medical school approved by the Council on Medical Education and Hospitals of the American Medical Association. The subject of the competition will be "Recent Advances in the Recognition, Treatment and Control of Poliomyelitis."

As in the previous competition, the purpose is to encourage good medical writing as well as to promote the collection of scientific material, and particular weight will therefore be given to such qualities as clarity, simplicity and general literary distinction. The conditions of the contest are unchanged: manuscripts should be between four and five thousand words in length, clearly typewritten in English, double or triple spaced, with references listed at the end in numerical sequence according to the form used by the *Quarterly Cumulative Index Medicus*. Papers must be in the hands of the editor by March 15, 1950. All manuscripts will become the property of the *Journal*.

The prize for the best essay among those submitted for consideration will be \$100. The paper will again be published in the "Medical Progress" series, and the author will receive a hundred free reprints.

The second prize will again consist of a two-year subscription to the *Journal*.

The prize-winning essay for 1949, entitled "Preventive Medicine," by Dr. Miriam D. Manning, of the class of 1949 at Tufts College Medical School, appeared in the June 30 issue of the *Journal*. It is hoped that the essays for 1950 will come up to the high standard set by Dr. Manning's essay, which demonstrated the quality of medical writing that physicians should be capable of and which the judges unanimously awarded first prize.

By the influence of a pretended clairvoyant mesmerizing female over vulgar minds, an elaborate and patient examination of the manure of a large stable was recently made in Boston, to find the body of a missing expressman, whom she declared had been murdered, and was there concealed. On Monday, of last week, the defunct reappeared in the city, in excellent condition!

Boston M & S J, September 26, 1849

MASSACHUSETTS MEDICAL SOCIETY



DEATHS

LANG — Walter E. Lang, M.D., of Westboro, died on September 11. He was in his sixty-sixth year.

Dr. Lang received his degree from Hahnemann Medical College and Hospital of Philadelphia in 1910. He was a member of the New England Society of Psychiatry and the American Psychiatric Association and a fellow of the American Medical Association.

His widow, a daughter and a son survive.

MANDELL — Augustus H. Mandell, M.D., of New Bedford, died on September 3. He was in his eighty-second year.

Dr. Mandell received degrees from New York University Medical College in 1897 and Cornell University Medical College in 1899. He was resident physician at Sassaquin Sanatorium in New Bedford.

His widow survives.

McFEE — William D. McFee, M.D., of Haverhill, died on September 7. He was in his seventy-fifth year.

Dr. McFee received his degree from University of Vermont College of Medicine in 1897. He was president of the American Academy of Physical Medicine and was a fellow of the American Medical Association.

His widow, four daughters and two sisters survive.

CORRESPONDENCE

STUDY OF TWINS

To the Editor The study of twins is of great value in providing information concerning the respective importance of hereditary predisposition and environmental influences in disease in man. The results of the use of this method have shown a hereditary predisposition to tuberculosis, diabetes and tumor formation, and a high, medium or low intelligence quotient.

There is some *a priori* evidence of a hereditary predisposition for peptic ulcer. Only 6 cases of peptic ulcer in either or both of monozygous or dizygous twins have been reported in the readily accessible literature. Since twins are born in 1 of 86 births and identical twins in 1 of 344 births and the general incidence of ulcer is from 5 to 10 per cent, there should be plenty of material available.

I should like to ask physicians to co-operate in assembling such material by sending me information regarding cases in which one or both twins develop peptic ulcer, the site of the ulcer, the age of the patient at onset of the ulcer, the type of twins (monozygous or dizygous), the sex and date of birth of the twins and the number and age of the brothers and sisters and the absence or presence of ulcer in each.

A. C. Ivy, M.D.

Department of Clinical Science
University of Illinois

DIFFICULTIES OF GENERAL PRACTICE

To the Editor Having recently made the transition from one of the larger teaching hospitals to a rural general practice, I feel called upon to comment on your editorial of August 11 entitled "Education of the Family Physician."

As one of a bewildered group of young men who have recently finished medical school, I was faced with the problem of specialization. My environment and conditioning has been such that, seemingly, the man who was in general practice was a man who had unsuccessfully competed for some type of residency and so was ungracefully thrust out into the world to make a living with the unspecialized knowledge that he had managed to accumulate. I, too, had been guilty many times of referring patronizingly on hospital records, to the "L M D."

However, with the passage of time and the increasing size of my family, it soon became apparent that I should not be able to go on with my training—that soon I must earn a living. And medicine had reached the stage where it could be said that the "renaissance of the general practitioner" was upon us. There was the increasing agitation by the American Medical Association for more general practitioners, specialization had begun to be viewed with alarm, there had been created a General Practitioner of the Year Award, and a new group, the American Academy of General Practice, had made its appearance. It is in this favorable era that I have begun my general practice.

And after four months of rural general practice I believe that I can begin to make some comments on the status of my medical education. First and foremost, it is not advancing as it used to. The editorial referred to above glibly states that "The family doctor is likewise to blame by trying to do too much and becoming so busy, he cannot keep up with attendance at meetings or with medical literature. Instead he would do well to put such educational activities on a required list each week." When one works seven days a week for twelve to fourteen hours and more a day, one finds it difficult to keep up with what is going on. My journals are only glanced through because I find myself too busy. Is it the patients' fault? I don't know. Perhaps in a while the novelty of "the new doctor" will wear off. But what I am getting at is that, through apparently no fault of my own, I have become too busy and don't know what to do about it. One can hardly refuse to see patients in an area like this if they call one.

Secondly, educational opportunities for the rural practitioner, particularly in this area, are almost nil. There are no hospitals that contain ward beds for me to visit and observe. What shall I do? When one is located hundreds of miles from teaching centers, getting to them is more easily said than done, especially if one dare not leave because of critically ill patients who cannot be turned over to anyone during one's absence.

Finally, membership in the American Academy of General Practice, a purported stimulus to education, excludes the neophyte who is just beginning his practice. He must have completed three years of general practice before being considered for membership. This hardly leads to encouragement for a man to continue his education if he is excluded from the few educational opportunities that may be open to others but not to him, simply because he has not "put in enough time" to become a member. And, in three years, who knows whether the requirements for membership will have been made even more rigid and I, and men like me, will be unable to qualify for membership. Yesterday there was no American Board of Proctology.

What is the answer? Certainly, it cannot be that the general practitioner in an area like this is at fault. Perhaps it is society, or perhaps it is the physicians themselves who have banded together and made tight centers of learning, meccas toward which many of us aspire but for the nonce are unable to enjoy. There are many like myself, I am sure, who would like to be heard. There must be because my colleagues who are near me have the same problems. Are we to blame for our stagnation? Perhaps I am rationalizing when I say, "No."

M ROBERT KNAPP, M D

117 Saunders Street
La Plata, Missouri

BOOK REVIEWS

Psychiatry A short treatise By William A O'Connor, L M S S A (Lond), D P M (Lond) 8°, cloth, 380 pp Baltimore Williams and Wilkins Company, 1948 \$9.00

For an adequate review of this textbook one would need to know not necessarily the literature and history of the development of psychiatry as practiced in Great Britain, but rather the attitude and emotional reaction toward psychiatry and its therapeutic approach as manifested by the psychiatrists of today. The author states, both in the preface and in the body of the text, that his approach is that of psychosomatic medicine. The impression is gained, however, that here is a man torn between two worlds: the organic and the functional, or the descriptive and the dynamic analytical.

On the whole, the material is well organized. Too often, definition of terms and mechanisms are left to haphazard search on the part of the beginner. The chapter on "Symptoms of Mental Disease" and that on "Psychic Mechanisms" are a distinct step forward in the understanding of a new subject. To present the various paranoid reactions as a group is probably well justified and leads to clearer thinking, although one still must consider it a type of schizophrenia, as long as the official classification continues, and the author rightly does so. "Analytic Therapy and Theory" is also a logical introduction inasmuch as the author tends toward an eclectic approach. Other than the above, the general outline of each chapter devoted to each of the major groups of the psychoses (namely "History," "Aetiology," "Psychopathology," "Symptomatology," "Diagnosis," "Prognosis" and "Treatment") is systematic and conducive to clear thinking.

Only a beginner can tell what a beginner gets out of an introductory text to psychiatry. Had there been no effort by the author to set forth a thesis, one would have little to remark about, either for originality or lack of it. As it is, there is the curious feeling that the past still influences too much, that description takes the place of dynamics, that psychiatry is still the handmaiden of neurology and that the functional is still overshadowed by the organic. Whether one or the other should prevail is entirely beside the point. One gets a little of the impression one does of "Lot's Wife." The author intellectually is walking into the future, but emotionally his face is turned to the past.

Conditioned Reflexes and Neuron Organization By Jerzy Konorski. Translated from the Polish under the author's supervision by Stephen Garry 8°, cloth, 267 pp, with 18 illustrations Cambridge, University Press, New York, Macmillan Company, 1948 \$4.00 (Cambridge Biological Studies)

This book undertakes the task of "attempting to extend the Sherrington conception of the functioning of the nervous system to the field of higher nervous activity." An effort is made to close the gap between Sherrington and Pavlov in the field of neurophysiology. The accomplishment is particularly commendable because the work was made much more difficult by the loss of original manuscripts and research notes as a result of war damage to the Nencki Institute of Experimental Biology in Poland. The material is presented in a clear, concise style when allowances are made for the fact that this is a translation from the Polish language. The translator should be complimented for the precise way in which he has executed his task. This short book is provocative and encourages a more adequate approach to the problem of higher cerebral integration. It definitely is a landmark for further research in the field of neurophysiology.

The author finds no conflict with the neuron theory of the functioning of the nervous system. The ideas developed in his research fall into the framework of this theory. However, the point is presented that the activity of the cerebral cortex is associated not only with the idea of excitability and the inhibition of transmission of impulses but also with new paths for these stimuli to travel on their complicated journey.

Three assumptions are made to account for these properties. The first is that "the elaboration of a condition reflex consists in the formation of new connexions in the brain, or rather that there can be the formation and multiplication of synapses between coupled cerebral centres." Secondly, it is postulated that if "a combination of excitations which results in a plastic change is not repeated within a certain period,"

the regression of this change may occur. Thirdly, "internal inhibition being a process that arises with non-reinforcement of the established condition reflex consists in the formation of new synaptic connexions of an inhibitory nature, independently of the already existing excitatory synaptic connexions." Although an attempt is made to correlate the physiology of the higher nervous activity with neurophysiology, the author well recognizes the limitations of his own presentation, several of which he mentions. He states that he is concerned in this book with "lowest levels of cortical coordination" and that he has come up against many facts that because of their complexity are not fully covered by the principles he attempts to lay down. He presents a challenge of trying to understand cortical and subcortical cerebral function in relation to human mental activity. He seems to believe that the physiology of the higher nervous activity is now at the stage that physics reached several centuries ago.

The format of the book is good, and a good index covers a rather general table of contents. The reader is able to become familiar with much of the Russian literature, which is difficult to translate. In spite of some of the verbosity that may be attributed somewhat to the difficult task of translation, this book is recommended for those who are interested in the complicated field of cerebral physiology.

Reproduction and Survival By R. Christie Brown, M.B., M.S., F.R.C.S., F.R.C.O.G. 12^o, cloth, 108 pp. London: Edward Arnold and Company, 1948. \$2.25.

In this remarkable monograph, the author presents a well known British obstetrician's concept of the philosophy of reproduction as a means of racial survival, viewing embryology as a biologic phenomenon. Reproduction is a racial, not an individual, process whose objective is to guarantee survival of the species. In the contest for survival, in which the individual is merely a pawn in the game, various patterns of reproduction, adapted to the environment, have been employed. Civilization mitigates some of the stresses of nature in the struggle to live in a highly hazardous and competitive universe, and physical death is deflected by the rejuvenation of tissues at reproduction. But civilization introduces new hazards of its own, and medical science sometimes makes possible the temporary survival of the unfit and the perpetuation of undesirable qualities. Abundant reproduction, continuous variation and unhampered natural selection are the essentials of racial survival and evolutionary improvement amid the thrusts and parries of a dangerous world. To a certain limited extent parental care, co-operation and sacrifice may substitute for free reproduction, but declining human birth rates are the danger signals of progressive racial deterioration and decay. The only physical immortals are the species and the germ cells, the fateful race of zygotes. Man, who alone has developed an organism capable of harboring spirit, is more concerned with the individual than with the species, but nature is concerned only with the survival of living forms.

*So careful of the type she seems,
So careless of the single life*

Dementia Praecox: The past decade's work and present status. A review and evaluation. By Leopold Bellak, M.D. With a foreword by Winfred Overholser, M.D. 8^o, cloth, 456 pp., with 8 illustrations. New York: Grune and Stratton, 1948. \$10.00.

As stated in the subtitle, Dr. Bellak presents in this work a review and evaluation of the work of the past decade concerning the problem of schizophrenia. He presents a well systematized and readable review of all the major investigative work that has been done in the past ten years, and correlates the numerous isolated facts from both the organic and the psychogenic standpoints concerning the etiology, psychogenesis and psychopathology of schizophrenia. In addition, he gives a well integrated evaluation of the various forms of therapy and technique.

This work presents in one volume the results of extensive research concerning this problem and therefore provides a valuable summary of present knowledge of schizophrenia. The volume should be of great value to those interested in this problem and of equal, if not greater, importance to those who are initiating their study of schizophrenia, presenting

as it does a complete summary of existing knowledge and directing the reader's attention to future avenues of investigation.

Muscles: Testing and function. By Henry O. Kendall and Florence P. Kendall. 4^o, cloth, 278 pp., with 162 illustrations. Baltimore: Williams and Wilkins Company, 1949. \$7.50.

This atlas on the testing and function of muscles is refreshingly clear and easy to read. The photographs of the contracting muscle on the subject are excellent and give a vivid picture of the movement performed. The muscles of the upper and lower extremities, the back, the abdomen and face are shown and described in turn. For completeness, one would have liked to see a fuller description of the muscles of the eye and the buccal cavity. But the testing and training of these muscles is probably outside the function of the physiatrist. There is a concise descriptive text accompanying each photograph. There are charts of the origin and insertion of the varying inner ration of muscles. The methods of recording muscular efficiency are carefully described. This work appears at an appropriate time when there is renewed interest and improved techniques for the rehabilitation of the handicapped. Its careful arrangement and illustration should recommend it for the training and guidance of physicians and physiotherapy technicians as a valuable guide in assessing physical disabilities. The Kendalls are to be congratulated for producing so useful and pleasing a treatise.

Present Concepts of Rehabilitation in Tuberculosis. A review of the literature, 1938-1947. By Norvin C. Kiefer, M.D., M.P.H. 8^o, cloth, 398 pp. New York: National Tuberculosis Association, 1948. \$3.50.

This book is a compilation of the literature on the subject of rehabilitation of the tuberculous. Fifteen of its sixteen chapters are abstracts of the current literature, and the last chapter is devoted to the comments of the author. This literature has sprung up chiefly in the past decade or fifteen years. It deals with the extent of this problem, the eligibility for rehabilitation services, suitable work for ex-patients, the contagious aspect of the disease and so forth. The administration as well as the cost of such a program also receives attention. The psychologic and the spiritual aspects of dealing with the chronically ill are also considered.

Although much has been written on rehabilitation and the author has abstracted more than a thousand articles, very little has actually been accomplished. This subject lends itself very well to lengthy discussions and seminars, but the actual concrete program of rehabilitation in the full sense of the word is beset with many difficulties. The protean nature of this disease and the contagiousness as well as the higher age of the present-day sanatorium population are major obstacles. However, the National Tuberculosis Association, through its state and city organizations, has dedicated itself to this task and made rehabilitation one of its goals. At least the community is made aware of its responsibilities to the handicapped person. Much education will be required on the part of labor unions and industries, as well as in legislative halls, regarding compensation laws, for the problem of employment of the handicapped to be solved.

This book is comprehensive in its scope and deals adequately with the new and very difficult subject of rehabilitation. The author knows his subject and speaks with authority on the various phases of a complicated and difficult process. This book should prove useful to all tuberculosis workers.

The Story of Medicine. By Joseph Garland, M.D. 8^o, cloth, 259 pp., with illustrations. Boston: Houghton Mifflin Company, 1949. \$2.75.

In this short work the author has not undertaken a complete, systematic history of medicine, like those by Fielding Garrison and Cecilia Mettler. Rather, in a series of twenty-two editorial essays, he presents a popular synopsis review of the evolution of medical practice and science from the time of the prehistoric medicine man to the present day of specialists, of sulfonamides, of antibiotics, of blood fractionation and of radioactive isotopes. But he is concerned not merely with achievements but also with human personalities, and, without detailed biography, he recreates and revitalizes many "of the great physicians in the long line that has passed through the pages of medical history." Particularly is he to

be praised for the happy literary style of his work, and for his felicitous quotations from Homer, Martial, Shakespeare, "Everman" and others. The book is well illustrated with twenty-three admirable original line drawings by Erwin Austin, and has a bibliography of thirty-two well selected titles. We are indeed fortunate to possess this fascinating volume by the editor of the *New England Journal of Medicine*.

Clinical Auscultation of the Heart By Samuel A Levine, M.D. and W. Proctor Harvey, M.D. 8°, cloth, 327 pp., with 286 illustrations. Philadelphia: W. B. Saunders Company, 1949. \$6.50.

This book brings to the student and the general practitioner the results of a long and fruitful experience in cardiovascular auscultation. It is divided into four major sections: heart sounds, cardiac irregularities, cardiac murmurs and miscellaneous auscultatory findings. The last include fifteen conditions in which auscultation may be useful. The title is more restrictive than the subject matter, since the discussion is by no means limited to auscultation. Treatment, for example, is outlined for all the cardiac arrhythmias and the x-ray findings in the congenital anomalies are described. Phonocardiograms are used very freely, but are correlated with electrocardiograms and with no other reference tracings such as phlebograms, which are essential in the analysis of diastolic phenomena. The illustrations are at times so reduced in size, and the sound tracings recorded at such slow speed, as to give little indication of the value of qualitative phonocardiography with modern techniques. This however, does not detract from the sound, clinical basis of the book. If the reader masters the stethoscopic technique, the auditory discrimination and the fundamental logic of these authors, most of the conditions described will not require graphic analysis. Outstanding are the discussions of gallop rhythms and systolic murmurs. The book can be recommended as a valuable guide to anyone aspiring to auscultatory perfection.

Lung Dust Lesions Versus Tuberculosis By Lewis G. Cole, M.D. 4°, cloth, 474 pp., with 428 illustrations. White Plains, New York: American Medical Films, Incorporated, 1948. \$10.00.

The author is a prolific writer and investigator of the old school, combining practical clinical knowledge with pure science. For years he has pioneered in the field of roentgenology. More recently, his chief interest has been the pathology of the lungs as related to pneumoconiosis. He writes in a very delightful conversational style that makes for easy reading.

This is not a book on dust lesions or on tuberculosis as applied to its clinical aspects. The author deals chiefly with the intricacies of pathological interpretations of dust lesions in the lungs such as silicosis, tuberculosis and silicotuberculosis. According to him, many dusts other than silica cause lung dust lesions. In persons exposed to coal, talc, iron, copper, beryllium and so forth, inhalation of such dusts, especially if they are also laden with micro-organisms, may cause fibrosis of the lungs. He also insists that chronic infections of the lungs and even tuberculosis cannot be distinguished pathologically from silicosis by the conventional light-field method of present-day microscopical examination. He believes that only by use of cross polaroid technique or cross nikols, especially lighted with a technique evolved by him, can silicosis be definitely distinguished from tuberculosis. He also deprecates the fact that patients with silicosis are kept from their occupations during the early stage of the disease, thus being unnecessarily deprived of their livelihood.

Many x-ray and pathological illustrations, excellently reproduced, accompany the text.

This book should be of particular interest to the research pathologist especially interested in the field of pneumoconiosis.

Considerable more research and orientation in the field of industrial medicine will be needed before the author's view can be accepted. He apparently loves a good argument, and he has left himself wide open for many a controversy.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Rheumatic Fever: Nursing care in pictures By Sabra S. Saller, R.N., consultant nurse, rheumatic-fever program, Virginia State Health Department and assistant professor of public-health nursing, Medical College of Virginia. 8°, cloth, 151 pp., with 204 illustrations. Philadelphia: J. B. Lippincott Company, 1949. \$3.50.

This manual on the care of children suffering from rheumatic fever is written primarily for parents. The methods of present-day treatment are explained in detail, and the illustrations are self-explanatory. It is intended as a guide, with the understanding that all care and procedures should be based on specific orders from the physician in charge. An introduction on rheumatic fever from a medical point of view is written by Dr. Reno R. Porter, assistant professor of medicine and director of the Cardiac Foundation of the Medical College of Virginia, and consulting cardiologist, Virginia State rheumatic-fever program. The remaining chapters, written by Mrs. Saller, who has been a special rheumatic-fever nurse with the Virginia Board of Health, since 1941, are devoted to the bed-rest treatment, personal care of the patient, care activities, diet, medications and treatment, and home teaching of school subjects. There is also a chapter on the social and emotional factors in the disease. The type and printing are excellent, but the ring type of binding is not suitable for a volume subject to hard usage. There is a good index. The manual should be in all public libraries and in the possession of parents with children suffering from rheumatic fever.

Clinical Aspects and Treatment of Surgical Infections By Frank L. Meleney, M.D., associate professor of clinical surgery, College of Physicians and Surgeons, Columbia University and associate visiting surgeon, Presbyterian Hospital, New York City. With a foreword by Allen O. Whipple, M.D. 8°, cloth, 840 pp., with 287 illustrations. Philadelphia: W. B. Saunders Company, 1949. \$12.00.

This special work covers the whole field of surgical infections from head to foot. It is intended as a companion volume to the author's *Treatise on Surgical Infections*, published in 1948. The material is well organized, and the text is well written. Numerous case histories are interspersed throughout the text. Selected lists of references are appended to the various chapters. There is a comprehensive author-subject index of fifty-eight pages. The book is well published and should be in all medical libraries and available to all surgeons.

Obstetric Analgesia and Anesthesia: Their effects upon labor and the child By Franklin F. Snyder, M.D., associate professor of obstetrics and associate professor of anatomy, Harvard Medical School. 8°, cloth, 401 pp., with 114 illustrations and 18 tables. Philadelphia: W. B. Saunders Company, 1949. \$6.50.

This new work is essential for all obstetricians and anesthesiologists. The material is well arranged and well written. The text is divided into two parts: respiratory injuries of the child, and the treatment of pain during labor. The first part discusses in detail the respiratory injuries before birth, including intrauterine pneumonia, atelectasis and asphyxia. The second considers all the anesthetics used during labor. Lists of references are appended to the various subjects, and there is a good index. The book should be in all medical libraries.

Your Child or Mine: The story of the cerebral-palsied child By Mary L. H. Burton, executive secretary of the Westchester Cerebral Palsy Association. In collaboration with Sage H. Jennings. 12°, cloth, 64 pp., with illustrations. New York: Coward-McCann, Incorporated, 1949. \$1.25.

This small volume relates the case histories of 6 children afflicted with cerebral palsy. It is written for the laity and shows what can be done for such children, especially socially,

if they receive the proper attention. The text is concluded with a list of cerebral-palsy associations and clinics. The book does not attempt to prescribe medically or surgically for the children. There is a short glossary of terms and a list of books and articles for further reading.

Diabetic Menus, Meals and Recipes By Betty M. West 8° cloth, 254 pp. Garden City, New York: Doubleday and Company, Incorporated, 1949. \$2.95.

This dietary manual was written primarily for diabetic patients and their families. Mrs. West acquired her knowledge at first hand, since she is a diabetic housewife. The soundness of her cookbook is attested by Dr. Rypins, a well known authority on diabetes. The book is well published, and there is a good index. It should prove valuable to those for whom it was written.

NOTICES

ANNOUNCEMENTS

Dr. Edmund F. Finnerty, Jr., announces the opening of his office for the practice of dermatology at 482 Commonwealth Avenue, Boston.

Dr. Aldo A. Luisada announces his appointment as assistant professor of medicine and program director of cardiology at University of Chicago School of Medicine, 710 South Wolcott Avenue, Chicago 12, Illinois, and the termination of his practice at 483 Beacon Street, Boston, on October 1, 1949.

Dr. William A. Lynch announces the opening of an office for the practice of obstetrics and gynecology at 1101 Beacon Street, Brookline, Massachusetts.

Dr. Albert O. Seeler announces the opening of an office for the practice of internal medicine at 1 Craigie Street, Cambridge.

SUFFOLK DISTRICT WOMAN'S AUXILIARY

The first meeting of the 1949-1950 season of the Suffolk District Woman's Auxiliary will be held on Thursday, October 6, at 2:30 p.m., in Sprague Hall, Boston Medical Library. The speakers will be Dr. A. J. A. Campbell, president of the Suffolk District Medical Society, and Miss Mary Jo Kraft, health education consultant for the United States Public Health Service, whose subject will be "How Doctors' Wives Can Help in the Tuberculosis Detection Campaign." Tea will be served after the meeting.

GREATER BOSTON MEDICAL TECHNOLOGISTS ASSOCIATION

A meeting of the Greater Boston Medical Technologists Association will be held in the lecture hall of the Boston Lying-in Hospital, 221 Longwood Avenue, Boston, on Tuesday, October 4, at 7:30 p.m. Dr. T. Hale Ham will speak on the subject "The Mechanism and Diagnosis of Hemolytic Anemias."

VETERANS ADMINISTRATION COURSE IN CLINICAL ELECTROCARDIOGRAPHY

A course in clinical electrocardiography will be given by Dr. David Littmann at the Veterans Administration Hospital, West Roxbury, Massachusetts, on Fridays from 4 to 5 p.m., beginning October 7.

Interested physicians and new students are invited.

NEW YORK ACADEMY OF MEDICINE

The Twenty-Second Graduate Fortnight of the New York Academy of Medicine will be held October 10 through 21, the subject being "Advances in Diagnostic Methods." The program includes morning panel discussions, afternoon hospital clinics, evening addresses and scientific exhibits and demonstrations.

Fellows of the Academy will be furnished registration cards without application. For others, a registration card will be sent upon receipt of check for ten dollars, payable to the Academy, and forwarded to New York Academy of Medicine, 2 East 103rd Street, New York 29, New York.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3-6 Association of Medical Illustrators. Page 472 issue of September 22.

OCTOBER 3-MAY 19 Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286 issue of August 18.

OCTOBER 4 Boston City Hospital House Officers' Association. Page 472 issue of September 22.

OCTOBER 4 Greater Boston Medical Technologists Association. Notice above.

OCTOBER 6 Suffolk District Woman's Auxiliary. Notice above.

OCTOBER 7 Veterans Administration Course in Clinical Electrocardiography. Notice above.

OCTOBER 10-21 New York Academy of Medicine. Notice above.

OCTOBER 11-15 American Society of Clinical Pathologists. Drake Hotel, Chicago.

OCTOBER 13 Moonucleosis. Dr. Andrew Contratto. Peotucket Association of Physicians. 8:30 p.m. Haverhill.

OCTOBER 14 Tuberculosis Rehabilitation Society. Page 434 issue of September 15.

OCTOBER 19 Massachusetts Chapter of American Academy of General Practice. Page 434 issue of September 15.

OCTOBER 24-26 National Gastroenterological Association. Page 251 issue of August 11.

OCTOBER 24-28 American Public Health Association. Page 251 issue of August 11.

OCTOBER 28 Massachusetts Psychiatric Society. Page 434 issue of September 15.

NOVEMBER 2 New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 2-5 Pan American Congress of Pediatrics. Page 251 issue of August 11.

NOVEMBER 3-5 American Association of Blood Banks. Page xi issue of June 16.

NOVEMBER 7-9 National Society for Crippled Children and Adults. Page 184 issue of July 28.

NOVEMBER 7-12 International College of Surgeons. Page 251 issue of August 11.

NOVEMBER 14-17 American Academy of Pediatrics. Page 251 issue of August 11.

NOVEMBER 16 Massachusetts State Society of Examining Physicians. Page 324 issue of August 25.

DECEMBER 28 and 29 American Association for the Advancement of Science. Page 350 issue of September 1.

FEBRUARY 20-23 American Academy of General Practice. Page 252 issue of August 11.

MAY 16-18 Massachusetts Medical Society Annual Meeting. Hotel Statler, Boston.

JULY 17-22 International Congress for Scientific Research. Page xvii issue of September 1.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 6

THURSDAY OCTOBER 6

2:30 p.m. Suffolk District Woman's Auxiliary. Sprague Hall, Boston Medical Library.

FRIDAY OCTOBER 7

*9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*12:00 p.m. X-Ray Conference. Margaret Jewett Hall. Mount Auburn Hospital, Cambridge.

*1:30 p.m. Tumor Clinic. Out Patient Department. Mount Auburn Hospital, Cambridge.

*4:00-5:00 p.m. Veterans Administration Course in Clinical Electrocardiography. Veterans Administration Hospital, West Roxbury.

MONDAY OCTOBER 10

*11:30 a.m.-12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleveland Floyd to charge.

*12:15-1:15 p.m. Clinicopathological Conference. Mayo Amphitheater, Peter Bent Brigham Hospital.

TUESDAY OCTOBER 11

*12:15-1:15 p.m. Cholecystoenterological Conference. Peter Bent Brigham Hospital.

*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*Open to the medical profession.

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NATIONAL HEALTH SERVICE—RECOMMENDATIONS OF THE HOOVER COMMISSION*

HUGH R. LEAVELL, M.D., D.R.P.H.†

BOSTON

FORMATION of the Commission on Organization of the Executive Branch of the Government, more widely known as the Hoover Commission, was authorized by the eightieth Congress. Its duties were to investigate activities of the Executive Branch with the objectives of limiting expenditures as far as possible consistent with proper performance of essential services, doing away with overlapping and duplication, consolidating similar services and abolishing unnecessary ones, and defining the limits of executive function. The President appointed four members of the Commission, four were appointed by the President of the Senate, and four by the Speaker of the House of Representatives. Twenty-three task forces or committees were set up by the Commission to study various federal activities. One of these was the Committee on Medical Services of which the Honorable Tracey S. Voorhees was chairman. The Commission was obviously not obligated to accept all the findings of its task forces. Major recommendations of the Committee on Medical Services, however, were accepted though the Commission itself divided on certain matters, some members presenting their views in minority reports.

Medical and public-health operations of the federal Government during the 1948 fiscal year cost one and a quarter billion dollars. Three major agencies spent most of this money: the Veterans Administration 61 per cent, the armed forces 20 per cent, and the Federal Security Agency 14 per cent. Of the total expenditure, 85 per cent was for direct medical care, 4 per cent for research, and the rest for public-health services, training and administration. Some 24,000,000 Americans are beneficiaries to a greater or less degree of the federal medical care program. Eighteen and a half million veterans make up the largest group and stand in a somewhat middle position between the 3,000,000 members of the armed forces with their dependents, in addition to merchant seamen for whom complete medical care is provided, and the 2,000,000 federal civilian employees receiving only an industrial health service.

Many more weaknesses were found in the medical care program of the federal Government than in public health and research. Some major weaknesses are especially noteworthy: agencies compete with each other for scarce personnel, hospitals are constructed without an over-all plan, and facilities available are not utilized to maximum efficiency. The quality of medical care provided by different agencies varies considerably. Congress has failed to define a clear policy on beneficiaries. The best use of private practitioners and university medical personnel is not made in the medical care program. Preventive medicine and research are not emphasized as they should be if the greatly increasing costs of medical care are to be reduced. Federal assistance needed so much by medical schools and other health-training institutions is lacking.

Since no one person is responsible for the over-all federal health operations, there is competition among agencies for scarce medical and technical personnel. At the time the report was made the Veterans Administration had 5600 beds closed because of insufficient personnel to staff existing facilities. In the armed forces the shortage is particularly acute with the idea general that a draft may be necessary to provide medical personnel, since voluntary recruitment is failing to meet the need. Even with a draft applying only to younger doctors, there would be a shortage of specialists.

Hospitals are being constructed by various federal agencies without relation to the plans or needs of other federal agencies or to those of voluntary, state and local governmental hospitals. Construction costs vary greatly, ranging from \$20,000 to as high as \$51,000 per bed, with the estimated cost to voluntary hospital construction at the present time about \$16,000 per bed. Nearly half the hospitals of the Veterans Administration are planned to be built in areas where experience has shown that staffing would be extremely difficult if not impossible. In a number of medical centers, it was found that various hospitals of the armed forces, the Veterans Administration and the Public Health Service showed definite lack of integration and waste both of plants and of medical personnel because there was no over-

*Presented at the annual meeting of the Massachusetts Medical Society, Worcester, May 24, 1949.

†Professor of public health practice, Harvard School of Public Health.

all plan for utilization. It was recommended that "hospital care for federal beneficiaries should be planned in relationship to the hospital resources of the country as a whole, not merely through construction of federal hospitals as a class apart."¹ Federal patients requiring hospitalization should be placed in nonfederal hospitals on a reimbursable basis instead of further enlargement of the federal hospital plant. In other words, nonfederal facilities being constructed under the Hill-Burton Act should be co-ordinated with the federal hospital system.

The quality of medical care available to beneficiaries of the federal Government varies greatly depending on which agency provides the service, whether or not facilities operated by this particular agency are readily available, whether sufficient technical personnel is at hand and so forth.

Congress has failed to define clearly its policy regarding beneficiaries of federal medical service. For example, veterans with nonservice-connected disabilities are entitled to hospital care under the vague authorization "if beds are available." As a matter of fact, 100,000 beds have been built to make them available for this group, since Congress has simply not faced the issue squarely. On the other hand, preventive services that might avoid subsequent costly hospitalization cannot be given to veterans without service-connected disability. Care for dependents of Army personnel is based on an authorization sixty years old providing that "whenever practicable" these dependents shall be provided with care. As a matter of fact, some 900,000 dependents of Army personnel are presently considered eligible.

The best possible use has not been made of highly skilled practitioners and personnel available through university medical schools. The Veterans Administration has made an excellent beginning and established a number of hospital programs in conjunction with medical schools, but this is a rather recent development and it certainly is fair to state that in general the objective has been to set up a full-time staff for federal hospitals with relatively little attention to the possibilities of utilizing part-time services from physicians serving the general public.

MAJOR RECOMMENDATIONS

To meet the weaknesses found, a united medical administration is recommended. This would be formed by consolidation of the major activities of the federal Government in medical care, medical research and public health, with an operating division in each of these principal fields. A division of staff services would provide for management, research, control of finance, personnel, supply and so on. Major activities to be included in the united medical administration would be medical care activities of the Veterans Administration, general hospitals and post or station hospitals (except those in isolated areas) of the armed forces within the con-

tinental United States, the entire Public Health Service, nonmilitary hospitals in the Canal Zone and the Food and Drug Administration.

The armed forces medical services would retain all responsibility for activities overseas, for military preventive medicine and for outlying post and station hospitals within the continental United States. Each of the forces would also retain a medical center for training and research. Medical care of Indians and federal prisoners would be provided by agencies presently responsible for these services, but united medical administration personnel would be assigned to work in these agencies. The Soldiers' Home, the Naval Home and health functions incidental to the operation of various federal agencies, such as the Atomic Energy Commission and the Tennessee Valley Authority, would not be included.

At the head of the united medical administration would be the ablest health and medical administrator obtainable. He and his top assistants would be appointed by the President and confirmed by the Senate. A career service for technical personnel would be developed on a basis somewhat similar to that now operating successfully for such personnel in the Veterans Administration. An advisory board to assist the administrator would consist of the Surgeons General of the Army and Navy, the Air Surgeon and the Administrator of Veterans Affairs. Congressional action is necessary to define clearly the beneficiaries entitled to governmental medical care and to prescribe ways in which this care should be made available.

Control of armed forces medical policies should be exercised by the Secretary of Defense. In each geographic area where members of the armed forces and others are operating under military control, responsibility for hospitalization and much of the outpatient care for all United States personnel in the area should be assigned to a single one of the armed forces.

Although there is obviously a need for federal assistance to medical and health education, it is indefinite to the point that a survey is required to determine the exact amount of federal assistance necessary.

"The necessity for medical care which requires heavy expenditures and much personnel, must not be permitted to result in minimizing the even greater importance of controlling disease."² Therefore, research, preventive medicine and public health are given the highest priority in the Commission's report. At numerous points in the report the idea is stressed that only by knowledge and application of new methods of controlling disease can the increasing costs of medical care be reduced.

INDEPENDENT HEALTH AGENCY

The Committee on Medical Services at first worked on the assumption that the Hoover Commission would recommend a combined department

of health, education and security. Later the Commission indicated that such a recommendation might not be made and asked the Committee what its reaction would be to an independent health agency. The suggestion was that such a plan might be preferable to the combined department. The Commission, in its final report, was divided on the question. It was pointed out that in a combined agency, co-ordination of health, education and security would obviously be simpler than in separate departments. The combined agency would meet the Commission's objectives of reducing the number of agencies reporting to the President to a manageable number. The tendency for overemphasis on professionalism would be reduced to a minimum in the combined organization. It was suggested by one member of the Commission that even if a separate agency were established for medical care, the public-health functions should be part of a combined department so that health activities relating primarily to state and local governments could be co-ordinated with similar programs operated by the federal Government in the fields of health, education and welfare. This type of arrangement, however, would separate curative and preventive health activities of the federal Government and would therefore be undesirable.

In an independent agency health functions would be segregated and not subject to irrelevant considerations relating to education and welfare. This might be desirable for certain other departments such as the armed forces, which would use medical services only. Health appropriations could be identified clearly as such. The implementation of special personnel policies considered necessary for the health field might be easier in a separate agency than if health were only one bureau of a combined department. In the separate agency pay and status of the top personnel would doubtless be higher and therefore more attractive than those of a bureau chief and his major subordinates in a combined department. It was suggested that even though a combination might eventually be desirable, the problem of integrating all the medical services to be included in the united health administration was such a great one that even if only as an initial step a separate agency would be desirable.

VALUE OF PREVENTIVE MEDICINE

At many points in its report the Commission and the Committee on Medical Services stressed the importance of preventive medicine. All phases of the health program must receive proper emphasis if the best results are to be obtained. Medical care programs and medical research carried on by the federal Government must be related intimately to activities in public health and preventive medicine. As new procedures are made available by research they must be incorporated promptly into practice. The public must be told what is available and induced to obtain

for themselves the benefits of modern medical science. In this way members of the health team concerned with diagnosis and treatment of disease should be relieved of an increasing part of their heavy burden. With the passage of time it may be that people will more and more come to regard disease as a result of failure to apply available knowledge rather than as the result of bad luck.

At the moment it is extremely difficult to estimate with any accuracy possible savings in the cost of illness that could be accomplished through full use of all present knowledge of disease prevention. Health and productivity are intangible values, and it is unprofitable to attempt complete separation of prevention and treatment since one merges imperceptibly into the other. Incomplete statistics of illness rates also complicate the problem. Some direct costs of illness may be computed fairly satisfactorily, such as doctors' bills, medicines and hospitalization, in addition to wages lost because of illness and potential earning power lost through premature death. However it is difficult to compute the cost to industry of idle machines and impairment of productivity of other workers by absence of the sick man.

As of 1948 expenditures for medical care were estimated at \$8 000 000 000 per year, and the loss in output due to disease and injury estimated at \$27 000 000 000 annually. How much of this amount could be saved if all known preventive measures were applied to the fullest possible extent and if research were supported at the optimum level to make new methods of prevention, health promotion, medical care and rehabilitation available as rapidly as possible? Of course, no one can answer this question. However, the results would undoubtedly be astounding. A few examples of what may be accomplished by preventive measures will give some indication of the results that might be expected.

Industry — Employers report that a first class medical and safety department will reduce occupational disease 63 per cent, absenteeism 30 per cent, compensation cost 29 per cent, and labor turnover by 27 per cent.

Armed Forces — Various types of vaccination, plus sanitation and DDT, made losses due to typhoid fever, small-pox, typhus, cholera, plague, yellow fever and tetanus negligible. Malaria was a minor problem within the U. S. and responded satisfactorily to vigorous control measures in the Pacific. Through x-ray screening at induction centers 150 000 cases of tuberculosis were kept out of the armed forces and the tuberculosis incidence among the forces and among veterans since the war has been only about one tenth that of World War I. Deaths from disease were a much smaller proportion of total deaths than in any previous war, with a 1:16 disease to battle death ratio in World War II, an approximately equal ratio in World War I and a 1:1 ratio in the Spanish War.

Cancer — If all the 334 000 new cancer cases each year had the best modern treatment in states possible with early diagnosis we might anticipate about 200 000 five-year cures contrasted with about 9000 from the average type of treatment given after cancer becomes widespread.

Tuberculosis — Based on 1945 standards the annual cost of tuberculosis to the nation is estimated at \$56 million dollars. If we were willing to spend only \$1 million more each year for ten years it is estimated that tuberculosis

could be so reduced that only 37 million a year would be needed thereafter to keep it under control

Malaria — The estimated 2 million cases a year cost some 500 million dollars. Based on control programs around military areas during World War II, it is stated that with 53 millions spent over seven years malaria could be virtually eradicated so that only a quarter million a year would be needed thereafter to keep it under control

Maternal and Child Health — If the entire country had the infant mortality and maternal mortality rates of our best states, nearly 22,000 infants and 2100 mothers would be saved annually

Life Expectation — At birth, life expectation for white females is now 70.3 years having increased steadily by over 25 years since 1890 due largely to control of communicable diseases and better infant care. However, expectation at age 50 is increasing only slowly because diseases of later life have not yet been greatly affected by preventive measures. Based on experience of other countries, it is not at all unreasonable to hope for three or four additional years expectation at 50

If the 15 major causes of death during the productive period from 20-65 were completely eliminated, 178,500,000 years of productive life would be added for white males alone and life expectancy at 20 increased by 3.95 years

Some of the most important causes of death during this period are definitely amenable to preventive measures now available. A reasonably conservative estimate indicates that of the theoretically possible addition of 3.95 years, 1.95 could be achieved by full application of our present knowledge

SUMMARY

These are but a few examples of what preventive medicine can accomplish. Implementation of the Hoover Commission recommendations would provide a unified service giving proper emphasis to research and preventive medicine as well as to medical care

REFERENCES

1 Committee on Medical Services. Commission on Organization, Executive Branch of Government. *Medical Activities. Report to Congress*. 57 pp. Washington, D.C. U.S. Government Printing Office 1949
2 *Ibid* P. 30

PROCAINE PENICILLIN G FOR AQUEOUS INJECTION*

A Study of Blood and Urine Levels

MAJOR EDWIN J. PULASKI, M.C., U.S.A.,† AND CAPTAIN JAMES F. CONNELL, JR., M.C., A.U.S.‡

FT. SAM HOUSTON, TEXAS

RECENT developments in penicillin-therapy dosage schedules have resulted in numerous studies dealing with the significance of blood levels. The object of this communication is to report data concerning the blood plasma penicillin levels and urine concentration curves following intramuscular

administration of aqueous solution of procaine penicillin (Crysticillin)§

This procaine salt is relatively insoluble in aqueous solutions and body fluids, and this property forms the basis of a new principle in penicillin administration. It has been demonstrated that the addition of

TABLE 1 Levels of Crysticillin Assayed in Blood Serum and Urine after One Injection of 4000 Units per Kilogram of Body Weight

HOURS AFTER INJECTION	LEVEL							RANGE
	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	
	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc	
Serum								
1	0.6	0.3	0.62	0.31	2.5	1.25	2.5	0.31 - 2.5
3	0.6	0.6	1.25	0.31	0.62	0.31	1.25	0.31 - 1.25
6	0.6	0.6	0.62	0.31	0.31	0.31	0.62	0.31 - 0.62
12	0.0175	0.3	0.04	0.16	0.16	0.16	0.31	0.04 - 0.31
18	—	0.08	—	0.16	0.08	0.08	0.04	0.04 - 0.46
24	—	0.04	—	0.08	0.04	0.04	0.04	0.04 - 0.08
36	—	—	—	0.04	0.04	—	—	—
48	—	—	—	—	0.04	—	—	—
Urine								
3	200.0	200.0	321.0	72.0	240.0	220.0	230.0	72.0 - 200.0
6	200.0	200.0	225.0	160.0	210.0	230.0	220.0	160.0 - 200.0
12	200.0	120.0	50.0	120.0	200.0	166.0	210.0	50.0 - 200.0
18	*	200.0	19.5	23.0	100.0	133.0	166.0	19.5 - 200.0
24	76.0	21.0	0.6	50.0	*	45.0	2.1	0.6 - 76.0
30	20.0	21.0	0.6	23.0	*	19.0	1.6	0.6 - 230.0
36	0.4	1.6	0.05	21.0	23.0	2.1	1.0	0.4 - 23.0
48	—	0.05	—	3.4	1.6	0.8	0.8	0.4 - 3.4
54	—	—	—	0.1	*	—	—	—
60	—	—	—	0.04	—	0.8	0.8	—
72	—	—	—	—	—	0.8	0.8	—

*No specimen

*From the Surgical Research Unit, Brooke General Hospital, Brooke Army Medical Center

†Assistant professor of clinical surgery, Baylor University School of Medicine, chief of septic surgery and chief, Surgical Research Unit, Brooke General Hospital, Brooke Army Medical Center

‡Research associate, Surgical Research Unit, Brooke General Hospital, Brooke Army Medical Center

dried sodium carboxymethylcellulose to dry crystalline procaine penicillin G results in a stable suspension in diluents containing water. Sodium carboxymethylcellulose forms a viscous gel, which maintains

§The Crysticillin used in this study was kindly supplied by Dr. Charles H. Mann of E. R. Squibb and Sons, New York City

the procaine penicillin in discrete particulate suspension. This has eliminated the necessity for the use of oils.

A number of investigators have made a survey of this preparation, including Whittlesey and Hewitt,¹ Robinson et al.² and Stollerman and his associates.³

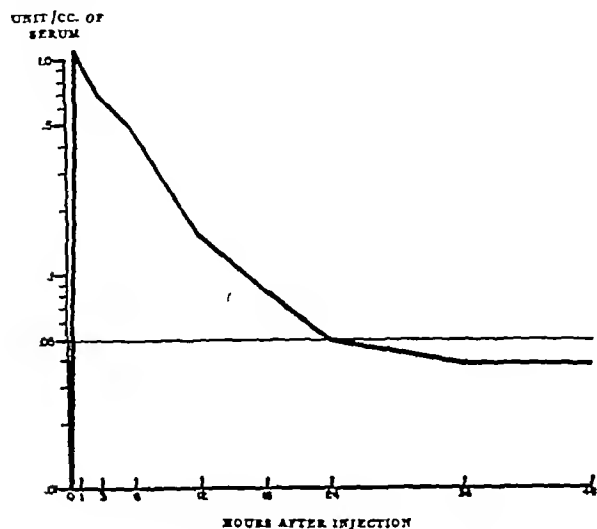


FIGURE 1 Mean Average Blood Level of Crysticillin in 7 Patients

According to Whittlesey and Hewitt, all subjects receiving an injection of 300,000 units showed demonstrable levels after twelve hours, and assayable levels were still demonstrable in three quarters of the patients after twenty-four hours. With a single injection of 600,000 units all subjects showed de-

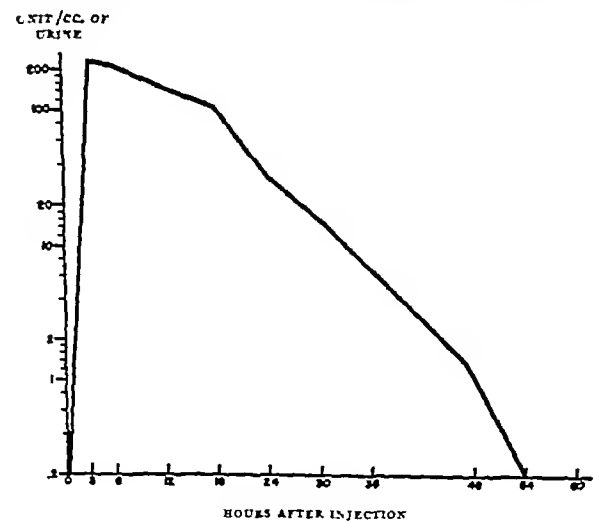


FIGURE 2 Mean Average Urine Level of Crysticillin in 7 Patients

monstrable levels at twenty-four hours. Our study is essentially a confirmation and extension of these findings.

MATERIALS AND METHODS

Procaine penicillin G (Crysticillin) is prepared for use by suspension of the powder in sterile distilled

water or sterile isotonic solutions of sodium chloride. This suspension has been administered to young male adults in one, two or three injections on a

TABLE 2 Levels of Crysticillin Assayed in Blood Serum and Urine after Two Injections Eight Hours Apart

HOURS AFTER INJECTION	LEVEL				RANGE	
	CASE 1	CASE 2	CASE 3	CASE 4		
	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc	
Serum (first injection)						
1	0.63	0.3	0.16	0.16	0.16	- 0.63
3	1.25	0.3	0.3	0.16	0.16	- 1.25
6	0.63	0.3	0.16	0.08	0.08	- 0.63
Serum (second injection)						
8	0.63	0.16	0.16	0.08	0.08	- 0.63
9	1.25	0.3	0.3	0.3	0.3	- 1.25
11	0.63	0.08	0.3	0.3	0.08	- 0.63
14	0.63	0.16	0.3	0.3	0.16	- 0.63
20	0.3	0.16	0.16	0.16	0.16	- 0.3
26	0.16	0.08	0.08	0.16	0.08	- 0.16
32	*	0.02	0.02	0.16	0.02	- 0.16
44	*	—	—	0.08	0.02	- 0.08
Urine (first injection):						
3	333.0	416.0	219.5	223.0	219.5	- 416.0
6	375.0	*	100.0	242.0	100.0	- 375.0
Urine (second injection)						
8	250.0	374.0	200.0	233.0	200.0	- 374.0
11	291.0	416.0	250.0	217.0	217.0	- 416.0
14	375.0	291.0	374.0	225.0	225.0	- 375.0
20	333.0	291.0	291.0	225.0	225.0	- 333.0
26	225.0	250.0	333.0	150.0	150.0	- 333.0
32	100.0	70.0	250.0	125.0	70.0	- 250.0
44	7.8	60.0	225.0	*	7.8	- 225.0
50	3.4	14.6	90.0	7.2	3.4	- 90.0
60	12.0	*	60.0	*	12.0	- 60.0

*No specimen

basic dosage of 4000 units per kilogram of body weight. This approximates 1 cc per dose of 300,000 units per cubic centimeter of material.

Blood serum was assayed for penicillin by the Rammelkamp⁴ method using a strain of beta-

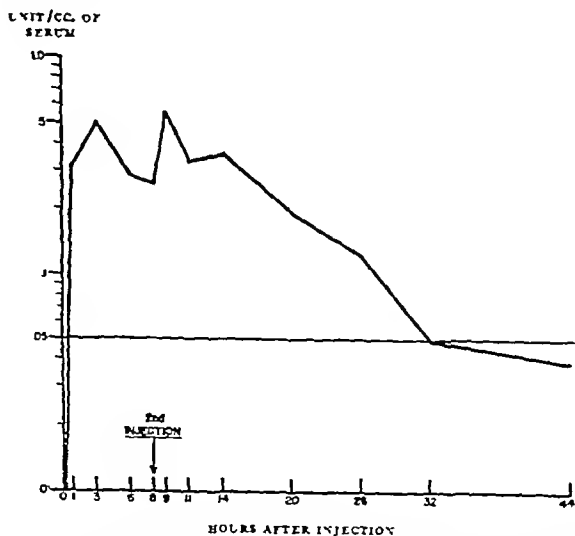


FIGURE 3 Average Blood Level of Crysticillin in 4 Patients Fifty Hours after the First and Forty-Two Hours after the Second Injection

hemolytic streptococci sensitive to 0.004 units per cubic centimeter of penicillin. The paper-disk plate method⁵ was employed to determine the level of

penicillin in urine A strain of hemolytic staphylococci sensitive to 0.06 units per cubic centimeter of penicillin was the test organism

RESULTS

A series of 7 patients received one intramuscular injection of 4000 units of aqueous procaine penicillin per kilogram of body weight (Table 1)

The blood levels obtained show that a peak level of 0.3-2.5 units per cubic centimeter of serum is

samples collected from these patients at the time that blood was drawn contained levels of penicillin in excess of 50 units per cubic centimeter for twelve hours after the penicillin injection The fluid intake was not restricted in any patient The urine contained penicillin for thirty-six hours after the in-

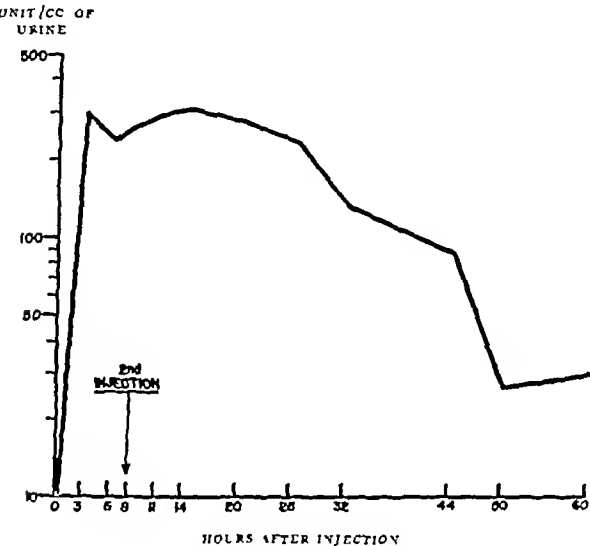


FIGURE 4 Average Urine Level of Crysticillin in 4 Patients Fifty Hours after the First and Forty-Two Hours after the Second Injection

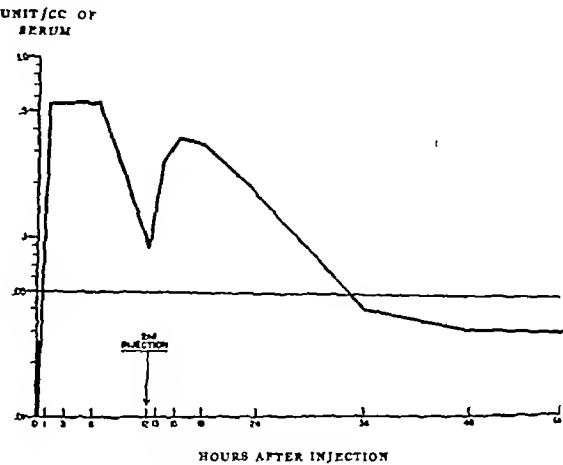


FIGURE 5 Average Blood Level of Crysticillin after the Second Injection

jected dose in all cases and at the forty-eight-hour period in a few

The mean average blood and urine levels obtained in this series of 7 patients are presented graphically in Figure 1 and 2 On this basis, it appears that significant penicillin levels are obtained in the blood for at least eighteen hours and in the urine for at least thirty-six hours after injection

achieved between the first and third hours after injection This was approximately halved six hours

A series of 4 patients were given a second injection of 4000 units of aqueous procaine penicillin per kilo-

TABLE 1 Levels of Crysticillin Assayed in Blood Serum and Urine after Two Injections Twelve Hours Apart

HOURS AFTER INJECTION	LEVEL				RANGE	
	CASE 1 units/cc	CASE 2 units/cc	CASE 3 units/cc	CASE 4 units/cc	units/cc	
Serum (first injection)						
1	0.14	0.6	1.2	0.31	0.14	1.2
3	0.14	1.2	0.6	0.31	0.14	1.2
6	0.14	1.2	0.6	0.31	0.14	1.2
Serum (second injection)						
12	0.07	0.07	0.07	0.16	0.07	0.16
13	0.14	0.14	0.56	0.31	0.14	0.56
15	0.56	0.14	0.56	0.31	0.14	0.56
18	0.56	0.28	0.28	0.31	0.28	0.56
24	0.14	0.14	0.14	0.31	0.14	0.31
36	<0.0175	0.035	<0.0175	0.08	<0.0175	0.08
48	<0.0175	—	—	<0.04	—	—
60	<0.0175	—	—	—	—	—
Urine (first injection)						
3	>200.0	>200.0	>200.0	72.0	72.0	>200.0
6	200.0	>200.0	>200.0	89.0	89.0	>200.0
Urine (second injection)						
12	92.0	>200.0	>200.0	72.0	72.0	>200.0
15	>200.0	>200.0	*	78.0	78.0	>200.0
18	100.0	>200.0	*	78.0	78.0	>200.0
24	17.5	96.0	400.0	160.0	17.5	400.0
36	96.0	84.0	166.0	50.0	50.0	166.0
42	7.9	68.0	*	*	7.9	68.0
48	1.1	*	25.0	23.0	1.1	25.0
60	<4	*	5.8	<0.4	<0.04	5.8
72	—	*	<0.4	—	—	—

*No specimen

after injection, and assayable levels were present at eighteen hours in 4 of the 5 specimens tested Urine

gram of body weight eight hours after the first injection Results as shown (Table 2) reveal that

assayable serum levels are present eighteen hours after the second injection and twenty-six hours after the first injection in all patients. Assayable urine levels are present fifty hours after the first and forty-

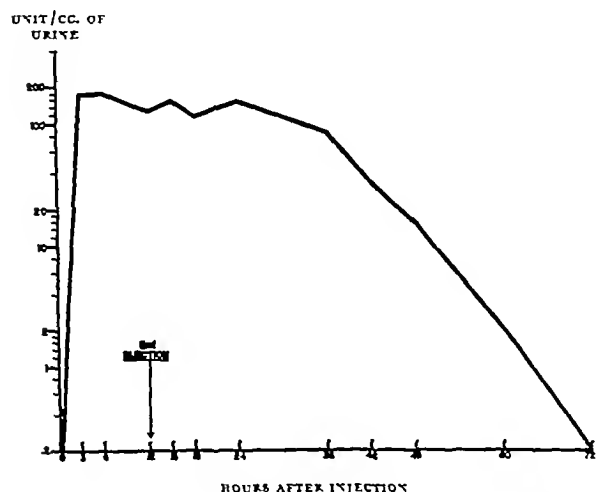


FIGURE 6 Average Urine Level of Crysticillin after the Second Injection

two hours after the second injection of 4000 units. The average blood serum and urine levels are illustrated in Figure 3 and 4.

Another series of 4 patients received a second injection of 4000 units of aqueous procaine penicillin per kilogram of body weight twelve hours after the first injection. The results (Table 3) indicate blood

at least thirty-six hours after the second injection (Fig 6).

Blood serum and urine assays also were determined in a series of patients receiving large single doses of Crysticillin, as follows: 10,000 units per kilogram of body weight in 5 patients (Table 4), 12,000 units in 4 patients (Table 5), and 16,000 units in 5 patients (Table 6 and Fig 7 and 8). All

TABLE 5 Levels of Crysticillin Assayed in Serum and Urine after One Injection of 12,000 Units per Kilogram of Body Weight

HOURS AFTER INJECTION	LEVEL				RANGE
	CASE 1	CASE 2	CASE 3	CASE 4	
Serum	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc
1	1.15	1.2	6.1	4.0	1.15 - 6.1
3	1.4	3.5	5.5	3.25	1.4 - 5.5
6	0.7	1.4	5.5	2.75	0.7 - 5.5
12	0.4	1.0	1.87	1.92	0.4 - 1.92
24	0.3	0.16	0.34	0.4	0.16 - 0.4
36	0.2	0.2	0.19	0.4	0.19 - 0.4
48	—	0.16	0.16	0.16	— - 0.16
Urine					
3	160.0	190.0	190.0	205.0	160.0 - 205.0
6	140.0	200.0	180.0	150.0	140.0 - 200.0
12	125.0	178.0	160.0	150.0	125.0 - 178.0
24	130.0	68.0	100.0	70.0	68.0 - 130.0
30	105.0	11.3	47.5	20.3	11.3 - 105.0
36	100.0	0.8	6.25	0.8	0.8 - 100.0
48	80.0	—	0.96	—	0.96 - 80.0

TABLE 4 Levels of Crysticillin Assayed in Serum and Urine after One Injection of 10,000 Units per Kilogram of Body Weight

HOURS AFTER INJECTION	LEVEL					RANGE
	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	
Serum	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc
1	6.7	2.4	1.15	1.15	0.9	0.9 - 6.7
3	5.0	2.2	1.60	1.70	1.25	1.25 - 5.0
6	5.0	1.5	2.50	1.60	1.5	1.5 - 5.0
12	1.0	0.6	0.9	0.9	0.93	0.6 - 1.0
24	0.8	0.2	0.24	0.62	0.2	0.2 - 0.8
36	0.2	0.3	0.3	0.05	0.03	0.03 - 0.3
48	0.3	—	0.04	—	—	0.04 - 0.3
Urine						
3	180.0	210.0	180.0	180.0	140.0	140.0 - 210.0
6	61.1	140.0	200.0	180.0	200.0	61.1 - 200.0
12	72.2	120.0	160.0	200.0	160.0	72.2 - 200.0
24	2.1	100.0	120.0	25.0	30.0	2.1 - 120.0
36	0.96	25.0	100.0	1.0	37.0	0.96 - 100.0
48	0.20	0.8	21.0	0.8	0.09	0.09 - 21.0

levels in all patients twenty-four hours after the first and twelve hours after the second injection, 2 of the 4 patients had assayable blood levels eighteen hours after the second injection (Fig 5). In all patients, assayable levels in the urine were present

patients had blood serum levels after more than thirty-six hours. Urine levels in excess of 10 units per cubic centimeter were found in all patients thirty-six hours after injection, and assayable levels

in excess of 1 unit were present in most cases at forty-eight hours.

No local or systemic reactions occurred in any of the patients during or after the administration of the drug.

SUMMARY

Three dosage schedules of aqueous procaine penicillin were studied in three groups of patients

aqueous procaine penicillin per kilogram of body weight were administered intramuscularly to three groups of patients In all patients assayable blood

TABLE 6 Levels of Crysticillin Assayed in Serum and Urine after One Injection of 16,000 Units per Kilogram of Body Weight

HOURS AFTER INJECTION	LEVEL					RANGE
	CASE	CASE	CASE	CASE	CASE	
	1	2	3	4	5	
	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc
Serum						
1	4 06	1 1	3 75	2 75	2 5	1 1 - 4 06
3	4 37	3 5	4 5	4 0	3 3	3 3 - 4 5
6	5 0	1 4	3 87	1 6	1 6	1 4 - 5 0
12	3 75	1 0	2 5	0 7	0 9	0 7 - 3 75
24	0 62	0 16	0 7	0 16	0 3	0 16 - 0 7
36	0 19	0 19	0 16	0 3	—	0 16 - 0 3
48	—	0 16	—	—	—	— 0 16
Urine						
3	170 0	190 0	250 0	145 0	145 0	145 0 - 250 0
6	195 0	200 0	165 0	130 0	125 0	125 0 - 200 0
12	150 0	178 0	150 0	125 0	110 0	110 0 - 178 0
24	100 0	68 0	125 0	25 0	30 0	30 0 - 125 0
30	82 0	11 3	110 0	0 8	2 9	0 8 - 82 0
36	32 5	0 8	70 0	—	0 8	0 8 - 70 0
48	0 96	—	5 9	—	—	0 96 - 5 9

comprising young adult males With a dosage of 4000 units per kilogram of body weight, assayable levels were detected in the blood and urine at least eighteen hours and thirty-six hours, respectively, after intramuscular injection In each case when the dose was repeated eight hours later assayable blood levels were present twenty-six hours and assayable urine levels fifty hours after the first injection

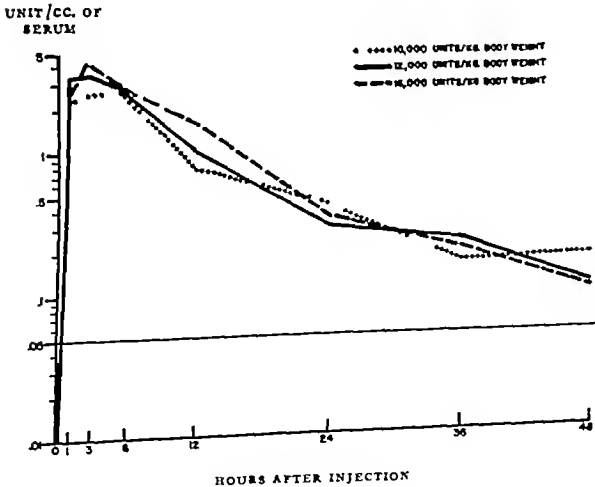


FIGURE 7 Average Blood Level of Crysticillin after Various Doses of the Drug

tion In patients receiving the same initial dose at intervals of twelve hours blood levels were present in all patients twenty-four hours after the first injection and in 2 of the 4 patients thirty-six hours after the first injection The urine still contained penicillin forty-eight hours after the first injection Single doses of 10,000, 12,000 and 16,000 units of

levels could be determined for thirty-six and urine levels for forty-eight hours

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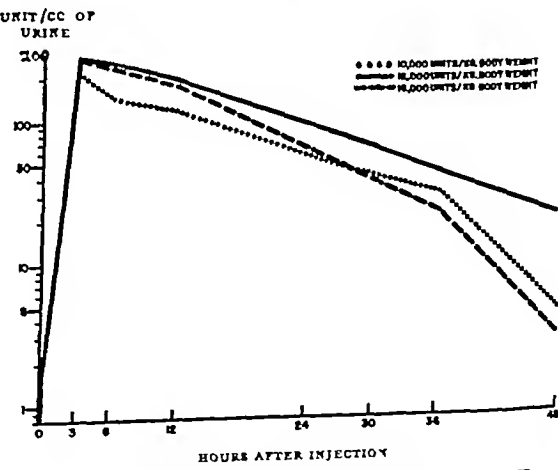


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- 3 Stollerman G H Roston E H and Toharsky B. Guide to use of procaine penicillin in hospital practice *New York State J Med* 48:2501-2505 1948
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- 5 Loo Y H et al. Assay of streptomycin by paper-disc plate method *J Bact* 50:701-709 1945

THE USE OF PSYCHOTHERAPY IN GENERAL PRACTICE*

LEO ALEXANDER, M D †

BOSTON

PSYCHOTHERAPY is part of medical practice. As with any useful medical procedure it should not remain limited to the specialist's office. Like all medical procedures, psychotherapy contains elements of art as well as of science.

In the practice of psychotherapy actions and attitudes are frequently more important than words. Emotionally sick adult people have a good deal in common with children, in particular the fact that their complaints and abnormal actions frequently express their feelings and problems in a symbolic rather than a direct manner, that they both frequently distrust words, that they learn more from example and the opportunity to identify themselves with good leadership than from precept, and that they relate themselves to the world more through emotional experience than according to instruction. Thus, how the doctor acts toward the patient, how he listens to him and how he speaks to him is often more important than what he tells the patient. It is frequently of greater value to offer new good interpersonal experiences than new thought content, although both are inextricably interwoven.

In its most elemental and nonverbal form, psychotherapy can be carried out successfully even on animals.^{1, 2} It is obvious that in the treatment of animals attitudes and actions play the main part, since animals do not understand words. But the ability to influence animals or human beings by attitudes and actions is the most important natural gift of the psychotherapist.

If I were asked to devise a screening test by which candidates gifted for psychotherapeutic work could be discovered, I should say that the person most likely to become a good psychotherapist was the type of person to whom stray dogs take easily, who could effectively gain the confidence of beaten dogs or who could easily ride an anxious horse that was sensitive to the bit and that customarily shied at the slightest provocation. I should place much more emphasis upon these faculties and attitudes, which are inherent as well as acquired than upon theoretic psychodynamic knowledge. The psychotherapist must constantly keep in mind that his actions and his attitudes are at least as important as his words.

Once the principle has been understood the technics can be learned. They fall essentially into

the following groups: supportive treatment, ventilation, shift of emphasis, interpretation, and reassurance. It is of particular importance, of course, to know the limits of these various forms of psychotherapy and to know when to add other methods such as medicinal forms of treatment or when to refer patients to a specialist for more intensive abreactive or interpretive psychotherapy or for the various forms of shock treatment, such as electric shock or insulin coma treatment³ to modify successfully abnormal emotional or mental states.

MAIN PSYCHOTHERAPEUTIC TECHNIQS

Supportive Treatment

The main element of supportive treatment is the doctor's attitude. Irrespective of whether the patient comes to him with a physical ailment or with a neuropsychiatric disease manifested by physical complaints, it is of fundamental importance that the doctor listen to the complaint, take it seriously and subject the patient to a thorough physical examination. The thoroughness of an examination frequently determines the success of supportive treatment. The effect of such treatment is, of course, enhanced by the doctor's reputation in the community — by his standing as a professional man and citizen. Both a doctor's reputation and his thoroughness enhance each other, conversely, it can sometimes be disastrous if a well qualified and highly respected physician takes the complaint of the patient lightly and because of his initial impression and shortage of time subjects him to a hurried and superficial examination. This can increase the feeling of rejection at the hands of life, which may be the main factor in the neurosis of an unsuccessful man or a rejected, unloved woman or child. The doctor must give, by his attitude and actions, the assurance to the patient that he cares for him, that he is interested in him and that he is eager to help him. There is an old saying that "a specialist is a man who does a rectal examination." I should like to paraphrase this and say that a psychotherapist is a physician who takes a complete and thorough history and who does a complete and thorough physical examination.

The degree to which such an attitude is psychotherapeutic was recently brought home to me by a patient who consulted me in a state of severe anxiety. This forty-six-year-old man complained of extreme nervousness, sweating pains throughout all bones of his body and attacks of weakness lasting several days at a time. He was very anxious and tense,

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	CASE	CASE	CASE	CASE	CASE	
	1	2	3	4	5	
	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc	unit/cc
Serum						
1	4 06	1 1	3 75	2 75	2 5	1 1 - 4 06
3	4 37	3 5	4 5	4 0	3 3	3 3 - 4 5
6	5 0	1 4	3 87	1 6	1 6	1 4 - 5 0
12	3 75	1 0	2 5	0 7	0 9	0 7 - 3 75
24	0 62	0 16	0 7	0 16	0 3	0 16 - 0 7
36	0 19	0 19	0 16	0 3	—	0 16 - 0 3
48	—	0 16	—	—	—	— 0 16
Urine						
3	170 0	190 0	250 0	145 0	145 0	145 0 - 250 0
6	195 0	200 0	165 0	130 0	125 0	125 0 - 200 0
12	150 0	178 0	150 0	125 0	110 0	110 0 - 178 0
24	100 0	68 0	125 0	25 0	30 0	30 0 - 125 0
30	82 0	11 3	110 0	0 8	2 9	0 8 - 82 0
36	32 5	0 8	70 0	—	0 8	0 8 - 70 0
48	0 96	—	5 9	—	—	0 96 - 5 9

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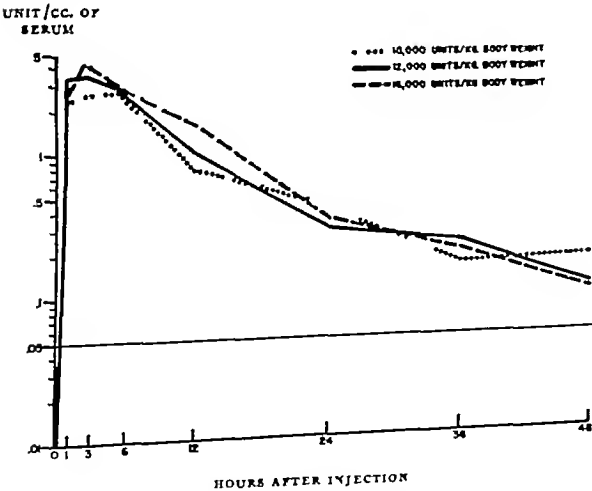


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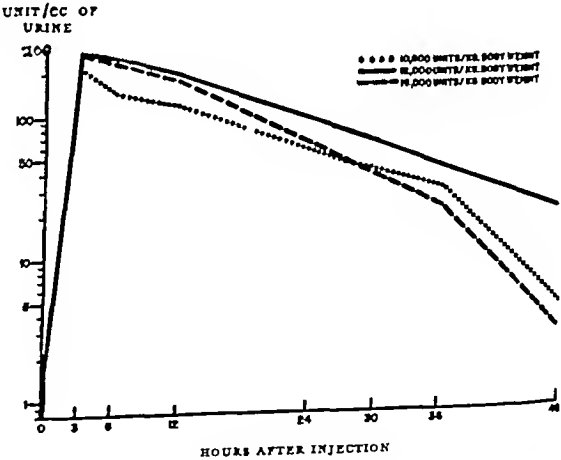


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and he was sweating profusely. He sat with his arms tightly pressed to his body. On the examining table his muscles seemed to be in a state of tension, and he had difficulty in relaxing them. He showed a markedly increased startle-pattern response, whereas all spontaneous motor activity was greatly reduced. It may be that I subjected this man to a particularly thorough neurologic examination because I wanted to be sure to find or rule out the existence of an organic neurologic condition, since he had suffered a blast injury, but the inadvertent psychotherapeutic effect of this detailed and painstaking examination was both surprising and delightful. As the examination progressed the patient gradually relaxed, and after it was over he was not only at ease but also cheerful and smiling. He departed in a state of apparent well-being. Without any direct psychotherapy, the acute anxiety state, obviously caused by the fear of having been seriously injured, melted under the impact of a thorough, sympathetic, careful examination, which was terminated by an encouragingly worded verdict of the finding of physical well-being. If this verdict had been rendered after a less painstaking examination, it might very well have aroused resentment and antagonism, followed by a build-up of anxiety and further discouragement. In other acute situational anxiety reactions, regardless of whether they express themselves in fear of injury by a serious accident or a fear of heart disease or any other physical ailment, the verdict of physical health will be acceptable to the patients only if they have been subjected to an examination that they accept as being of sufficient thoroughness, and the doctor must express by his attitude the fact that he has an open mind and that he is interested in finding out the truth.

Part of psychotherapy is teaching, and the most effective way of teaching is by example. If the physician wishes the patient to have an open mind and accept the truth, the patient must first be shown that the physician has an open mind and is interested in the truth himself. In a good relation the patient will unconsciously imitate the physician's own attitude. The arousal of mimesis is indeed the most important instrument of successful teaching, as well as of successful psychotherapy.

Of course, such reassurance cannot overcome a severe, deeply ingrained anxiety neurosis or a pre-psychotic panic, but an attitude of a wide-open mind and thoroughness will be helpful even in those conditions, although it may be then wise to withhold reassurance and interpretation until the patient himself is ready to accept them. Again, it is important to know one's limits. Unless the physician is very sure that the patient is ready to accept reassurance and interpretation, both of which must be used with great caution, it is much better to help the patient to stumble upon the solution by merely helping him with an attitude of thoroughness, open-mindedness and interest in the true state

of his health. It is important to realize that reassurance is not always real support. The anxious patient who believes that he is dangerously sick will more frequently regard reassurance as a brush-off and a lack of real interest on the part of the physician.

I once treated a young woman with a severe phobic state that had many features of an early schizophrenic psychosis with obsessive features. Nevertheless there was a great deal of meaningful material that prompted me to go on with psychotherapy. This patient had been to many doctors, including psychiatrists, and had left them all after a few visits. After a long course of treatment with many ups and downs, she finally became well fifteen months later. I then asked her, as I frequently do of recovered patients, what in her opinion was the most decisive therapeutic act to which she ascribed her recovery. Her answer was as follows:

When I went to you for the first time I did not like you, and I almost did not want to come back. When I came the second time I asked you a question — namely, whether I was actually out of my mind (I had the fear that I was going crazy or had actually gone crazy). When I asked you that you said, "I don't know. We have to find out first and then do the right thing about it." That gave me confidence in you. All the other doctors I had been to told me that I wasn't out of my mind and that I wasn't going to lose my mind, and I thought that they didn't understand me or they didn't tell me the truth. When you told me that you didn't know, I knew that I could have confidence in you, that you were honest and that you would always tell me the truth. From then on I kept coming back and I got well.

The answer I gave this patient had actually been the truth. After a number of interviews and equivocal tests I was not quite sure whether this was not an acute schizophrenic development that would be better treated with shock or insulin. The weight of evidence finally was in favor of a condition considered modifiable by psychotherapy, which turned out to be effective after some time. I knew it was the ring of truth in my statement that carried the weight. It is essential to realize that emotionally sick people, like children, have an uncanny sense of truth. This is particularly important in dealing with children. The ability of children to look through and size up their parents and others close to them is frequently equal to that of trained psychologists and psychiatrists. True supportive therapy can therefore never be given without the solid foundation of conviction of truth in what the therapist is saying. In supportive treatment one must definitely show that one is on the side of the patient in his battle with the world.

Ventilation

Next in importance to the supportive attitude is that of giving the patients the full opportunity and the setting of understanding approval in which they can freely ventilate their stresses and emotions. Once the patient is started in successful ventila-

tion, the physician should interrupt the patient as little as possible, but merely sit there with the understanding and encouraging smile of the statue of a wise Buddha. This technic is particularly helpful in certain cases of anxiety hysteria as well as in the anxiety states of the older age groups, especially those with hypertension. A good example of the former type is the case of a young married woman, aged thirty-five years, who came to my office in a state of marked distress and agitation, complaining of severe and persistent pain in her left cheek. She held her hand pressed against her cheek, stating that as soon as she released the pressure of her hand the pulsating became unbearable. This constant, throbbing pain had been present for three years. She had consulted a good many doctors, including two neurosurgeons and several dentists, about her complaint. Two weeks before referral to me, the patient went back to her first dentist, who took out an additional tooth (several had previously been extracted), which brought about no improvement. She was then referred to an otolaryngologist for investigation of her ears, nose and throat. He found no physical abnormalities that could be causing her complaint, and referred her for neuropsychiatric examination. She stated that this pain might be due to "something terrible" she had done in early life and that she had a guilty conscience that "bangs in the back of my mind." She then began to tell the grim history of her life. In the psychotherapeutic discussions with this patient I completely refrained from giving any interpretation, but instead merely helped her by occasional questioning to find the meaning of her symptoms herself. After the sixth interview her pain was gone, and recurred later only on two occasions for brief and meaningful periods after the twelfth interview. It remained absent after the thirteenth interview and did not recur at any time within three years of the sixteenth and final psychotherapeutic session.

An equally striking reaction to purely ventilative treatment occurred in a forty-six-year-old man who suffered from a chronic anxiety state with mild hypertension and symptomatic alcoholism. He had previously been refused insurance because of hypertension. When I first examined him, his blood pressure was 175 systolic, 80 diastolic. His wife had been on the verge of leaving him because of his drinking. Psychotherapy in this patient remained entirely ventilative in character. It appeared that he derived particular benefit from the opportunity to "blow off steam" regarding his resentment against his employers and business associates. There was remarkable gradual diminution of his anxiety as well as his hypertension. After three months of treatment his anxiety became sufficiently diminished that he felt able, without, of course, any implication of advice on my part, to take a step that he had wanted to take for many

years but had never quite dared to — namely to resign from his organization and to go into business for himself. Subsequently, his blood-pressure readings remained consistently normal, 130 systolic, 65 diastolic. His symptomatic indulgence in alcoholic beverages likewise improved, and he remained well and congenial with his family.

It is frequently observed that when ventilation proceeds on a purely intellectual level, without associated emotional expression, the therapeutic benefit is minimal or absent. The patients may tell their story, and at the end they may say, "This is my story, Doctor, but what does telling it do for me? I still feel the same way." It is then that one must bring about real emotional participation, an emotional reliving of the stress situation, for which the word *abreaction* has come into vogue, which literally means to react off or to "blow off steam."

I believe that the physiologic result of *abreaction* as a form of excitation can best be understood in Pavlovian terms. It is conceivable that the intense excitation of neurons associated with electric shock may be the extreme physical variant of the same principle. It appears that the bringing about of excitation, quite apart from the interpretation and working out of the emotional material, has in itself a wholesome effect, irrespective of whether the excitation was produced by the reliving of a recent crushing-threatening episode, by the bringing out of old resentments by verbalization, by reliving of emotional conflict, by the participation in exciting ritual or by the touching off of extreme excitation of the entire nervous system by an electric stimulus.

It must not be forgotten, however, that in spite of the strong physiologic components of the experience, the reliving and working out and the psychotherapeutic guidance and other forms of psychotherapy and understanding are of the greatest value. In spite of all the lip service given to the unity of mind and body, many physicians find it difficult to accept the fact that there is no separation of the psychologic and the physical aspects of treatments. Both should be utilized to the fullest for the recovery of the patient.

The more specifically psychotherapeutic technics consist of those which promote insight and which have to do with interpretation either directly or indirectly. The indirect method is preferable particularly for the beginner and in the beginning of psychotherapy. It is very important not to overwhelm the patient with interpretation and thereby to build up his defenses and resistances, but it is essential to feel out the patient before attempting to do so. It must be remembered that the scaling of strong defenses is a risky task, in psychotherapy as well as in war. The wise general or the wise psychotherapist will prefer a flanking movement, in the long run it will save time and risk.

Shift of Emphasis

The "flanking movement" that should precede direct interpretation and frequently is sufficient to take the place of direct interpretation is the shift of emphasis. By this I mean the subtle shifting of emphasis from the complaint or the apparent conflict to the more important material that the patient may have presented quite inadvertently without having been consciously aware of its import in relation to his complaint. The advantage of this technic is that it does not arouse antagonism and resistance. It is wise to take as a starting point something that the patient himself has told one.

A recent example is afforded by the case of a fifty-year-old man who reported to the outpatient clinic with a complaint of severe pain throughout the left side of the chest, for which he had first consulted the heart clinic, which referred him for neuropsychiatric consultation for the differential diagnosis of intercostal neuralgia or psychoneurosis. As frequently happens, the patient gave his problem away with the first sentence he spoke when he introduced himself. He said, "I want to explain to you why I come to this out-patient clinic instead of consulting a private doctor. I am a pharmacist, but I can't work in my line here in Massachusetts because my degree is not recognized here, but my wife wants us to live here because of our son. Therefore I have to work as a storeroom clerk and can hardly make enough money to get by." He then described with great vividness the pains in the left side of his chest. He felt deeply distressed and alarmed about them, and they were a very profound reality to him. Careful examination in addition to the clinical and laboratory tests done before convinced me that this patient was not suffering from organic disease. Furthermore, his marked state of anxiety and depression was positive evidence of an emotionally determined illness. On the other hand I believed that he would not take well to direct interpretation. At the conclusion of the examination, which I had carried out with great thoroughness, I imperceptibly shifted from the discussion of his complaints to that of his life situation. Very soon the patient was well in the process of discussing his impasse and obviously eager for what suggestions would be made. I dropped the hint that many illnesses improve provided the patient is happy or finds a way of being happy. Before long we were discussing ways of improving his life situation. It turned out that a compromise was feasible. A neighboring state was chosen where he could work in his own field and yet be sufficiently near his son to suit his wife. The mere possibility of doing something about his problem and the support implied in the assumption that he had a right to consider his own occupational happiness relieved him. In the course of readjustment of his life situation the pain vanished, and the danger of antagoniz-

ing the patient by the direct proffering of insight was avoided.

Interpretation

Although I refer here to interpretation of emotional illness, I believe it also holds true for physical illness that interpretation of the illness to the patient is an important part of medical management of the sick person. Interpretation is the most difficult part of psychotherapy, it requires the greatest amount of skill, tact and timing. It should not be attempted until one is very sure of one's ground and after one has established a good relation with the patient. The results are seldom as dramatic as those portrayed in the motion pictures. It is rather a slow process of understanding, and results from a continued co-operative effort of doctor and patient. Nevertheless, there are occasional cases in which a dramatic denouement may be achieved by a well timed interpretation for which the patient is ready. The most important thing is to interpret in terms acceptable to the patient. A genuine understanding of the patient is a prerequisite for such a procedure to be carried out successfully.

Even in insight-promoting treatment, actions and attitudes are an important instrument of therapy. The actions and attitudes that have been found beneficial and helpful on the basis of psychodynamic understanding are remarkably similar, even identical, with those derived from true religious attitudes. F. Alexander and M. T. French⁴ pointed out that the priest in Victor Hugo's novel *Les Misérables*, written as long ago as 1862, reformed the hero of the story, Jean Valjean, who had tried to rob him, by treating him with attitudes and acts of unexpected kindness, which constituted a masterpiece of brief psychotherapy. It is of fundamental importance that age-old spiritual insight and modern psychodynamic insight have led to the same conclusion: that certain thieves are deprived people who must first be given to before they can be reformed. It is likewise of interest in this connection that modern psychotherapy has rediscovered the value of love, in the spiritual sense of the word, as a therapeutic force.

Like all therapy that offers or suggests insight, even actions and attitudes if they serve that end are resisted by defenses to which the patient will cling until he becomes free enough to give them up. Thus, Jean Valjean's first reaction to the priest's kindness was one of a temporary recrudescence of his hostile behavior before he became able to give it up altogether. F. Alexander and French point out that even in this respect Valjean's reform conformed to the familiar rebounding pattern of response of a symptom or neurotic attitude to psychotherapy. This pattern also conforms to Pavlov's laws of the higher nervous activity of the cortex. In Pavlovian terms this initial negative reaction could be described as negative induction by a new

conditioned stimulus followed by positive induction that reinforces the stimulus sufficiently to allow it to irradiate. It appears that psychotherapy is a real force conforming to spiritual as well as to natural laws.

Reassurance

It is essential for reassurance that the patient believe that the doctor is truthful and that he has been sufficiently thorough to know whereof he speaks. In actual mental illnesses or severe neuroses, reassurance is of only secondary importance apart from its use as an adjunct to general supportive technic. Reassurance, however, is of great importance as a preventive measure. Irrespective of whether or not a physician chooses to treat overt neuropsychiatric conditions in his practice, there is one field in which he must do psychotherapy — that is, whenever he deals with chronic or incurable physical illnesses. In these conditions a great deal depends on the doctor's psychotherapeutic handling of the problem. The existence of such an illness constitutes severe neurosis-producing stress, and this superimposed neurosis or depression frequently makes the difference between an invalid and a reasonably active and well adjusted person. The way in which the physician handles such a problem may prevent, control or, on the other hand, sometimes even precipitate the superimposed neurosis. Thorough, warm understanding of the patient with a knowledge of his emotional needs will do a great deal to prevent superimposed neurosis in such cases. The problem begins with the way in which the diagnosis should be told to the patient. I personally favor giving the patient the true diagnosis, but in encouraging terms. Not telling the diagnosis sometimes makes the patients fear a worse possibility than even that which the well meaning physician has withheld. Another important point is to maintain in the patient a feeling of control — a feeling that he can do something for himself. Abandonment to fate constitutes extreme stress that few people, not even some of the most sturdy combat personnel in war, can take.

One should therefore never tell the patient "There is nothing I can do for you," without at least offering a program of things that he could do for himself and continuing to show a helpful interest. All too frequently such patients are abandoned to their own devices. The rationalization for doing so is usually a perfectly ethical one. The real motive, however, is more complicated. The chronically or incurably ill patient represents a tremendous challenge to the physician's opinion of his own healing abilities, which will frequently put him on the defensive, especially when the patient on his part enhances this challenge by openly hostile, demanding or critical attitudes. It is therefore understandable that in such a setting the doctor, espe-

cially when he is sensitive to criticism and hostility, may tell the patient that he can do nothing for him in such a way as to imply "There is nothing anybody can do for you," which to the patient means complete rejection and abandonment. It must never be forgotten that a principal function of the physician is to give hope to the patient and to relieve his relatives of responsibility by not dodging any responsibility himself.

It is also important to guard against an attitude of rejection in referring mental patients to a psychiatrist. The manner of the referral frequently determines success or failure of the patient's first contact with the psychiatrist and conditions his readiness to accept treatment. If the physician refers the patient with an attitude of rejection and detached disinterestedness in his problem, which to the patient implies "You are crazy, and you ought to go to a psychiatrist," he will go to the psychiatrist with a chip on his shoulder and co-operation will be difficult to obtain. If, however, the physician refers the patient to the psychiatrist in the same manner in which he would refer a patient to any other specialist, saying, for instance, "I want you to see my friend Dr. so and so, he is a specialist in this field, I am sure he will help you and I shall keep in close touch with him," the patient and his relatives will come prepared to have confidence and co-operation will result as a matter of course in a smooth and automatic manner.

CONCLUSION

I should like to conclude this paper with a few do's and don't's in the use of psychotherapy in office practice. In general one cannot go wrong with a warm supporting attitude, and in offering the patient opportunity for ventilation. If this ventilation should be associated with a marked emotional abreaction, the objective, supporting attitude must be maintained in the face of it, even if this abreaction should include the expression of hostility toward the physician. One should not interpret unless one is really sure of the ground — much damage can be done by novices.

If the patient improves only at the price of too much dependence on the therapist, or if he becomes dependent without improving, he should be referred to a person with more skill and experience in the field of psychiatry. It should be remembered that dependence is regression into an infantile state. Although the regression is sometimes necessary as a transitory phase during treatment, and frequently is undesirable even then, one must ultimately wean the patient and help him to mature. A physician of my acquaintance who rather prides himself on his self-taught skill in his psychotherapeutic management of neurotic patients told me once as a proof of his accomplishments that his cured neurotic patients retained so much confidence in him that for

years after treatment they would make no major decision without asking his advice, even in entirely nonmedical matters. To me this sounded as if a surgeon were taking pride in the fact that his patients were letting him dress their still-draining incisions for years after each operation. The primary goal must be kept firmly in mind to help patients to achieve health, happiness, maturity and independence. In every psychotherapy there comes the time when one must throw the ball of responsibility

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SYPHILITIC AORTITIS WITH OBSTRUCTION OF MULTIPLE AORTIC OSTIA*

WILEY F BARKER, M D †

BOSTON

UNTREATED or inadequately treated late syphilis is no longer so frequently seen by the average physician, and its exotic complications are becoming curiosities. The following case presents one of the more unusual cardiovascular complications.

CASE REPORT

S L (P B B H 7A850), a 52-year-old shipping clerk, was admitted to the Peter Bent Brigham Hospital on March 15, 1948, complaining of severe pain in the anterior part of the chest radiating down the left arm. This symptom had been present, especially on exertion, for about 10 months. The initial episode of pain had occurred while he was walking one evening, a sense of constriction in the chest and a pain in the left arm developed. After resting for several minutes he had been able to return home. Other attacks following a similar pattern became more severe and more frequent. Four months before admission he was admitted to another hospital for diagnostic studies.

Physical examination had revealed a markedly apprehensive man. There was a barely palpable radial pulse on the right, the left radial pulse was weak but palpable. The right carotid pulse was scarcely palpable, but the left carotid pulsation was full and bounding. There was no evidence of cardiac enlargement or other cardiovascular defect.

A positive serologic test for syphilis was obtained. Other blood examinations were within normal limits. An electrocardiogram was interpreted as showing myocardial changes, with a rate of 72 and nodal rhythm. The PR interval was 0.09 to 0.12 second, and the QRS complex was normal. RT was depressed in Lead I, V_4 and V_5 . The P waves were inverted in Lead 2 and 3 and upright in Lead 4. The T waves were diphasic in Lead 1 and V_5 , upright in Lead 2 and 3 and low in Lead V_4 .

The patient was discharged to the care of his physician with a diagnosis of anxiety state, angina pectoris, syphilis and a suspected congenital anomaly of the great vessels. Six million units of penicillin in oil was administered at home over the course of 10 days. There was no Jarisch-Herxheimer reaction and no subsequent reversal of the blood Hinton reaction to negative.

Symptoms continued, and the patient was given various medications including opiates, salicylates, Demerol, chloral hydrate and barbiturates without significant relief from pain. Nitroglycerin afforded only brief palliation. The severity and frequency of the attacks progressed until 4 days before admission, when the pain and sense of constriction became unremitting, with continued reference of pain down the arm, unrelieved by nitroglycerin. He had had no marked dyspnea,

orthopnea, ankle edema or cyanosis, but he had complained of profuse sweating and a sense of impending disaster. He was referred to this hospital by his physician.

Further past history was limited by the patient's inability to answer all questions. He had had no other significant illnesses and no operations. He denied any venereal disease other than gonococcal urethritis as a young man. He stated that as far back as he could remember he had had a small pulse in his left arm and an almost impalpable pulse in his right arm.

The patient was apprehensive and ashen faced, sweating profusely, and complaining of pain in the chest and left arm. The pupils were normal. No abnormalities of the nervous system were demonstrable. The chest was clear on the left, but on the right there was basal dullness, with diminution of breath sounds, bronchial breathing and moist rales. The right carotid pulsation was absent, a moderate pulsation was present in the left carotid. No pulse could be detected in the radial vessels on either side. Femoral and dorsalis pedis pulses were palpable but weak. The heart was not enlarged, the sounds were normal and without murmurs or friction rub. The abdomen was slightly distended, without fluid, and the liver edge was palpable but nontender three fingerbreadths below the costal margin. There was no abdominal tenderness.

The temperature was 101.8°F (by rectum), the pulse 104, and the respirations 30. The blood pressure was 0 in the arms and 100 systolic in the legs as determined by palpation of the dorsalis pedis.

Films of the chest taken at the bedside revealed a high diaphragm and a fairly marked degree of pulmonary congestion and edema. The heart appeared slightly enlarged to the right and to the left, although the right border could not be seen in its entirety. The aorta did not appear widened.

The urine was acid, with a specific gravity of 1.033. No albumin was found, but there was a + test for sugar and acetone. Rare red and white cells and hyaline casts were reported in the spun sediment. The hemoglobin was 15 gm per 100 cc, and the hematocrit 44 per cent. The corrected sedimentation rate was 21 mm per hour (normal, 15 mm). The white-cell count was 19,650, with 68 per cent neutrophils, 17 per cent band forms, 11 per cent lymphocytes and 4 per cent monocytes.

Electrocardiograms revealed an abnormal form of ventricular complex — the ST segment was depressed in Lead I and markedly depressed in Lead 2 and 3, the T wave was inverted in Lead 3. The unipolar limb leads showed an elevated ST segment, late inversion of the T wave in Lead AVR, elevated ST segment in Lead V_1 to V_3 and depressed ST segment in Lead V_4 to V_6 . These tracings were considered suggestive of infarction of the anterolateral aspect of the left ventricle, with subendocardial extension.

Three hours after admission the heart suddenly stopped, with continuation of respiratory movements for a few cycles. The diagnoses were coronary thrombosis with myocardial infarction, syphilis with suspected aortitis involving the coronary ostia, congenital anomaly of the aorta and possible dissecting aneurysm.

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At post-mortem examination, performed 3 hours after death, the body was that of a well developed and well nourished man. There was no peripheral edema. The abdominal cavity contained no free fluid. The liver weighed 2080 gm and was severely congested. The remainder of the gastrointestinal and genitourinary systems was normal.

There was bilateral hydrothorax, with 500 cc of clear, straw-colored fluid in the right pleural cavity and 350 cc in the left. There was no undue fluid in the pericardial cavity.

The heart weighed 380 gm and was not enlarged. The pericardium was normal. The right ventricular myocardium measured 0.3 cm, and the left ventricular myocardium 1.4 cm in thickness. There was a narrow layer of subendocardial infarction measuring 0.3 cm in thickness encircling the entire left ventricular cavity, with maximal changes anteriorly at a point midway between the base and the apex. The auricles were grossly normal. There was no evidence of valvular disease. The aortic ring showed no dilatation and no separation.

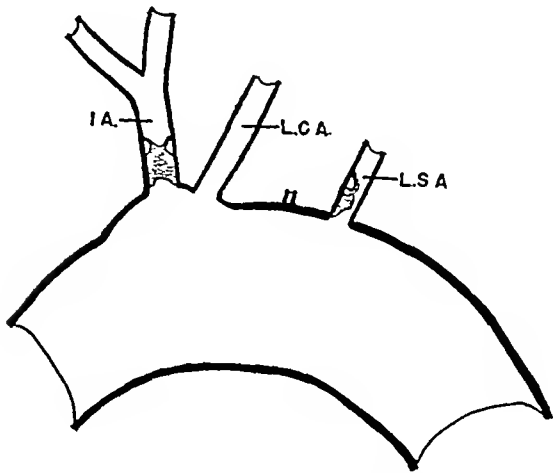


FIGURE 1 Longitudinal Section of the Aortic Arch and Its Branches, Showing Syphilitic Endarteritis

tion at the commissures. The measurements were as follows: tricuspid valve, 12 cm; pulmonary valve, 7.5 cm; mitral valve, 11 cm; and aortic valve, 6 cm.

The coronary arteries were patent throughout their course in the myocardium. At their ostia, however, there was marked thickening of the intima, which had almost obliterated the coronary orifice. At no other point in the course of the main coronary vessels and their main branches was there encroachment upon the lumen, although several small, yellowish atheromatous plaques were seen. The anatomic distribution and the origin of the arteries were normal.

The aorta arose from the heart in the usual manner and pursued a normal course throughout the chest. At the arch the innominate artery and the right common carotid artery arose in close proximity from the apex of a small, shallow outpouching of the superior surface of the arch, which measured 3.5 by 2.5 cm and was 0.7 cm in depth. The left subclavian artery arose from its normal position. Innumerable yellow plaques of atheroma were present from the level of the innominate artery down to the renal arteries. Most of these plaques were slightly elevated but intact; a few, however, were ulcerated. Between the atheromatous plaques in the ascending and descending aorta there was longitudinal wrinkling of the intima in a characteristic "tree-bark" pattern. The wall of the aorta was thickened except for the small outpouching described above and for a small disk-shaped area, 0.8 cm in diameter, in the mid-thoracic aorta where there was marked thinning. It was believed that the origin of the common carotid artery from the apex of the small aneurysmal pouch constituted an anomalous placement of this vessel.

The proximal portion of the lumen of the innominate artery was completely occluded by a smooth, adherent, pinkish-gray tissue. This occluding mass began about 0.5 cm from the orifice of the vessel and extended along its course for 1 cm. The distal surface of this obstruction was composed of two leaf-like cusps with a concavity directed distally (Fig. 1). Distal to this obstruction the vessel was patent, and bifurcated within 2 cm into normal common carotid and subclavian arteries, which followed normal paths into the root of the neck.

The orifice of the left common carotid artery was normal except for its displacement to the right, and for the fact that it was dilated, measuring 1 cm in diameter. It crossed the mediastinum and ascended into the neck in a normal position.

The left subclavian artery was markedly narrowed near its orifice by a valve-like piece of pinkish-gray tissue, similar to that obstructing the innominate artery, leaving a lumen less than 0.3 cm in diameter. The distal course and distribution of the left subclavian were normal. The superior and inferior thyroid arteries were greatly dilated and tortuous, measuring 0.3 cm in diameter.

The lungs showed some basal congestion. The principal microscopic findings of interest were limited to the heart and great vessels. The changes in the heart were



FIGURE 2 Section of the Innominate Artery, Showing Obliteration of the Lumen by the Intimal Proliferation and the Destruction of the Media (Elastic-Tissue Stain)

confined to the inner fourth of the wall of the left ventricle and were seen maximally in the interventricular septum, anterior left ventricle and lateral left ventricular wall. In this region there was an ischemic necrosis of the muscle fibers. There was disappearance and fragmentation of the nuclei in this zone. Minimal numbers of polymorphonuclear, lymphocytic and mononuclear cells were seen between the fibers. This was interpreted as a myocardial infarction of less than 4 days' duration. The remaining myocardium showed an irregularly

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The patient was apprehensive and ashen faced, sweating profusely, and complaining of pain in the chest and left arm. The pupils were normal. No abnormalities of the nervous system were demonstrable. The chest was clear on the left, but on the right there was basal dullness, with diminution of breath sounds, bronchial breathing and moist rales. The right carotid pulsation was absent, a moderate pulsation was present in the left carotid. No pulse could be detected in the radial vessels on either side. Femoral and dorsalis-pedis pulses were palpable but weak. The heart was not enlarged, the sounds were normal and without murmurs or friction rub. The abdomen was slightly distended, without fluid, and the liver edge was palpable but nontender three fingerbreadths below the costal margin. There was no abdominal tenderness.

The temperature was 101.8°F (by rectum), the pulse 104, and the respirations 30. The blood pressure was 0 in the arms and 100 systolic in the legs as determined by palpation of the dorsalis pedis.

Films of the chest taken at the bedside revealed a high diaphragm and a fairly marked degree of pulmonary congestion and edema. The heart appeared slightly enlarged to the right and to the left, although the right border could not be seen in its entirety. The aorta did not appear widened.

The urine was acid, with a specific gravity of 1.033. No albumin was found, but there was a + test for sugar and acetone. Rare red and white cells and hyaline casts were reported in the spun sediment. The hemoglobin was 15 gm per 100 cc, and the hematocrit 44 per cent. The corrected sedimentation rate was 21 mm per hour (normal, 15 mm). The white-cell count was 19,650, with 68 per cent neutrophils, 17 per cent band forms, 11 per cent lymphocytes and 4 per cent monocytes.

Electrocardiograms revealed an abnormal form of ventricular complex — the ST segment was depressed in Lead I and markedly depressed in Lead 2 and 3, the T wave was inverted in Lead 3. The unipolar limb leads showed an elevated ST segment, late inversion of the T wave in Lead AVR, elevated ST segment in Lead V₁ to V₃ and depressed ST segment in Lead V₄ to V₆. These tracings were considered suggestive of infarction of the anterolateral aspect of the left ventricle, with subendocardial extension.

Three hours after admission the heart suddenly stopped, with continuation of respiratory movements for a few cycles. The diagnoses were coronary thrombosis with myocardial infarction, syphilis with suspected aortitis involving the coronary ostia, congenital anomaly of the aorta and possible dissecting aneurysm.

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of a congenital defect, the presumptive explanation is that the obliteration of the great vessels had occurred early in the course of the disease when the patient was still a young man

SUMMARY

A case of syphilitic aortitis and endarteritis in which there was obliteration of the lumen of the innominate artery, partial obstruction to the lumen of the left subclavian artery and almost complete occlusion of the coronary ostia is reported. The patient pursued a steadily downhill course to die of myocardial infarction without actual coronary thrombosis, ten months after the onset of symptoms, and in spite of antisyphilitic therapy with penicillin.

The diagnosis of coronary-ostia disease should be more readily suspected when, in association with electrocardiographic changes of "global ischemia," there is evidence of other ostial obstruction, with or without a demonstrable aortic aneurysm. The current relative infrequency of late cardiovascular

manifestations of syphilis renders them nonetheless important.

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PUNCH LIVER BIOPSY IN THE DIAGNOSIS OF MILIARY TUBERCULOSIS

Report of a Case

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SINCE it is often difficult to substantiate a suspected diagnosis of miliary tuberculosis, an additional practical diagnostic procedure would be of value. As it is well known that miliary tubercles are scattered throughout the liver in this disease,¹⁻³ histologic study of a specimen of liver tissue would be of unquestioned value in confirming a clinical impression. In recent years punch liver biopsy has been established as a simple, practical and safe method of obtaining a specimen of liver tissue satisfactory for microscopical study and causes very little discomfort to the patient.⁴⁻⁵ Liver biopsy is not generally recognized as a method for the diagnosis of miliary tuberculosis, and since references to its use in the literature are scanty,⁴⁻⁵ it is the purpose of this paper to offer the procedure as a practical method for diagnosing the disease.

The technic of punch liver biopsy using either the subcostal or the intercostal approach has been ably reported by Hoffbauer,⁶ Volwiler and Jones,⁵ Popper et al.,⁵ Topp and his co-workers¹⁰ and others.⁷ The Roth-Turkel¹¹ and the Silverman¹² biopsy needles are those in most common use and yield quite satisfactory specimens for histologic examina-

tion. This material can also be used for culturing.⁹ The mortality of the procedure is extremely low if the usual precautions are taken, Topp et al.¹⁰ having recently reported a series of 350 liver biopsies without serious complications or mortality.

The following case, recently observed at the University of Virginia Hospital, illustrates the diagnostic value of this procedure in substantiating a suspected diagnosis of miliary tuberculosis.

CASE REPORT

A 26-year-old Negro had been well until 5 weeks before admission, when he first had a severe pleuritic pain in the right side of the chest. This was associated with a hacking cough, chills, fever, drenching sweats, anorexia and weight loss. A few days later he was admitted to another hospital, where he went progressively downhill and became critically ill and semistuporous. The temperature varied between 101 and 104°F. An x-ray film of the chest was reported as suggestive of miliary tuberculosis but was considered more consistent with a fungous infection. Penicillin, sulfonamides, aureomycin and a few doses of streptomycin were tried without effect, and the patient was transferred to the University of Virginia Hospital on March 15, 1949 for further studies.

Physical examination revealed an emaciated patient who appeared acutely ill. The other significant findings were in the chest. There was splinting of the right side of the thorax, with slight to moderate dullness up to the fourth and fifth ribs anteriorly. A few bubbling rales could be heard in the right base, and in the region of the right apex there were a few crepitant rales.

The temperature was 102°F, the pulse 95, and the respirations 25. The blood pressure was 110/70.

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scattered fibrosis, and many of the small arteries showed a hyaline intimal thickening encroaching upon the lumen.

The narrowing observed at the coronary ostia was due to a hyaline fibrous tissue containing an occasional lipoid-laden macrophage. There were many focal infiltrations with round cells. Some of these were found in the vessel walls near the junction of media and intima, the most marked infiltration was in the adventitia around the vasa vasorum. Sections taken through the site of obstruction in the innominate and subclavian vessels demonstrated a similar hyaline thickening of the intima, with focal infiltrations of round cells. The media of the innominate artery showed marked destruction and replacement with a vascular fibrous tissue (Fig 2 and 3),



FIGURE 3 Section of the Innominate Artery, Showing the Destructive Process in the Media under Higher Power (Elastic-Tissue Stain)

similar less marked changes were seen in the elastic tissue of the subclavian artery and the coronary arteries near their orifices.

Multiple sections through the aortic wall showed similar changes, focal infiltrations with round cells, especially around the vasa vasorum, marked intimal proliferation due to a hyaline fibrous tissue, and patchy irregular destruction of the elastic tissue of the media and replacement with a vascular fibrous tissue. There was intimal proliferation in the vasa vasorum. Small atheromatous pools were occasionally seen but contributed little to the over-all picture.

Levaditi's silver stains on all tissue blocks failed to reveal any recognizable spirochetes.

The final pathological diagnoses were as follows: syphilitic aortitis, with aneurysm of the terminal portion of the ascending aorta, syphilitic endarteritis involving the right and left coronary orifices and the orifices of the innominate artery and the left subclavian artery, subendocardial infarction of the left ventricle, cardiac failure as evidenced by passive congestion of the liver and abdominal viscera, and by bilateral hydrothorax, and anomalous origin of the left common carotid artery.

DISCUSSION

Stenosis of the coronary ostia with subsequent myocardial infarction is well described in the literature.^{1,5} Involvement of the coronary arteries in their course in the myocardium and involvement of other arteries of medium and smaller size is well known. The classic pathological picture is primarily an endarteritis of the vasa vasorum in the adventitia, with a secondary but nonsyphilitic intimal proliferation in response. There is also a marked destructive process involving the elastic tissue in the larger vessels, with replacement by fibrous elements.

In spite of the common pathological picture, there is difficulty in making the clinical diagnosis of ostial stenosis. Woodruff⁶ has cited this difficulty and has commented upon the rarity of myocardial infarction due to ostial stenosis in the absence of thrombosis. Associated thrombosis is usually on the basis of unrelated atheromatosis.

Obliteration of unilateral or bilateral radial pulsations is not uncommon in aneurysm of the arch, several recent reports have described the occurrence of a deficient pulsation in one or both upper extremities in association with syphilis and in the absence of a demonstrable aneurysm.^{7,8} In one of these cases,⁸ the pulse returned to normal after a course of arsenic therapy. No pathological material was presented.

Current observations⁹ indicate that adequate heavy-metal therapy usually results in the disappearance of the inflammatory process in aortitis. The place and efficacy of penicillin in the treatment of late cardiovascular syphilis is as yet undefined.^{10,11} Certainly 6,000,000 units of penicillin administered in the case reported above did not remove the evidences of active inflammatory processes although no recognizable spirochetes were to be found. It is perhaps confirmatory of the concepts of Moritz,¹ Saphir,² and Warthin⁸ that there was no regression of the secondary intimal proliferation, which was the actual obstructing agent in these vessels.

The electrocardiographic findings immediately prior to death were strongly suggestive of the total deficiency of the coronary supply as opposed to the solely focal changes more common in the usual atherosclerotic thrombosis. This case is being presented elsewhere as part of a series with electrocardiographic demonstration of subendocardial ischemia.¹²

In retrospect, then, it is possible to reach a diagnosis on the basis of the positive serologic test for syphilis, the unremitting angina and subsequent myocardial infarction, the aberrations of the pulses and the electrocardiograms suggesting "global ischemia." There is no satisfactory explanation of the patient's statement that he had always had deficient radial pulses. The pathological picture was clearly that of a syphilitic process and not that

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STUDIES ON THE RELATION OF PITUITARY-ADRENAL FUNCTION TO RHEUMATIC DISEASE*

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DURING the past few years it has become increasingly evident that the adrenal cortical hormones exert a marked influence on a wide variety of metabolic processes in man. The over-all effects exerted by these hormones may be divided into three general groups: an electrolyte-regulating effect, the regulation of the rate of utilization of carbohydrate, protein and fat, and an androgenic and anabolic effect.

NATURE OF ADRENAL CORTICAL ACTIVITY

Electrolyte-Regulating Effect of Adrenal Cortical Steroids

This is characterized by urinary retention of sodium and chloride, increased excretion of potassium, increased plasma and extracellular fluid volume.¹ It has also been shown that desoxycorticosterone-like steroids decrease the concentration of sodium and chloride in sweat.² The most potent electrolyte-regulating adrenal steroid is 11-desoxycorticosterone, which has been synthesized. The 11,17-oxysteroids (Compounds E and F) exert a relatively weak sodium-retaining effect³ (Fig 1).

Unfortunately, there is no direct measurement of circulating "salt" hormone. Therefore, the activity of such steroids must be estimated indirectly, by changes in the renal excretion of sodium, chloride and potassium, by alteration in the mineral composition of thermal sweat and by changes in hematocrit and body weight.

Regulation of Intermediary Metabolism by 11-Oxysteroids and 11, 17-Oxysteroids

The second group of metabolic activities modified by the adrenal cortex involves the regulation of

carbohydrate, protein and fat utilization, control of lymphoid tissue and circulating eosinophils. The administration of this type of compound is characterized by the following effects:

An increase in blood glucose level and liver glycogen stores.

An increased conversion of protein to carbohydrate (increased gluconeogenesis). Recent studies indicate that this effect is accomplished, not by an increased catabolism of body protein, but rather by diverting amino acid radicals to pyruvic acid and glucose (antianabolic effect).

An increased mobilization of depot fat and its enhanced utilization, thus sparing carbohydrate. An increased intestinal absorption of fat.

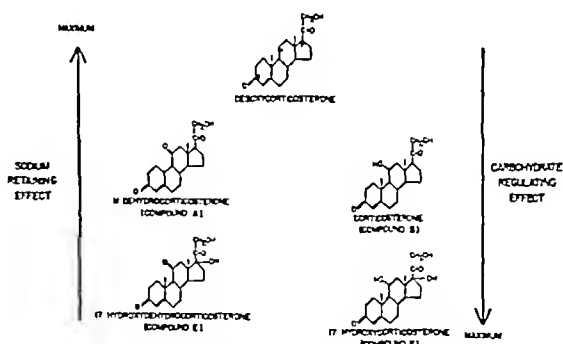


FIGURE 1 Relation of Chemical Structure to Sodium-Retaining and Carbohydrate-Regulating Effect

has been observed after the administration of this group of steroids, and although relatively unimportant calorically, it is of theoretical interest.

An increase in the renal clearance of uric acid, resulting in the excretion of large quantities of urate, both in normal subjects and in patients with gout.

A lysis of fixed lymphoid tissue and a transitory decrease in circulating lymphocytes. A somewhat more permanent effect is observed on the circulating eosinophils, which almost completely disappear from the blood during the period of action of the hormone.

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Examination of the blood showed a red-cell count of 4,300,000, with a hemoglobin of 13 gm., and a white-cell count of 5000, with 74 per cent neutrophils. Repeated blood cultures were negative. No acid-fast bacilli were found on several examinations of the sputum, gastric washings and direct bone-marrow smears. Specimens from each of these were also cultured for tubercle bacilli. Tuberculin and histoplasmin skin tests were negative, as were studies of the urine, stool and spinal fluid. Bone-marrow examination showed nothing pathognomonic, but there was an increase in plasma cells of 5 to 10 per cent.

X-ray films of the chest showed both lung fields to be involved with a miliary type of nodulation. When the examination was repeated 2 days later areas of miliary density were again seen scattered throughout both lung fields but were thought to be more suggestive of a fungous disease than of typical miliary tuberculosis.

The temperature ranged between 101 and 105°F, and the patient continued to look critically ill. Dihydrostreptomycin was started on the 3rd hospital day, since it was believed that the patient probably had miliary tuberculosis.

A punch liver biopsy was done on the 4th hospital day by the intercostal route, and the histopathological report* was as follows:

Throughout this liver tissue are many small lesions that are rather typical small tubercles. The center of the lesions contains some necrotic material, around the margins of the lesions epithelioid cells, numerous lymphocytes and an occasional giant cell can be seen. Special staining techniques for acid-fast bacilli reveal the presence of a few acid bacilli in these tubercles.

The diagnosis was miliary tuberculosis of the liver.

After the biopsy report the dosage of streptomycin was increased to 3 gm. daily, and promizole was begun in a dosage of 1 gm. every 6 hours. On the 6th day of streptomycin therapy the temperature started gradually down. The appetite began to improve and soon became enormous, the patient often consuming six large meals a day. Three blood transfusions were given to correct an anemia that had developed. At the end of the 4th week of hospitalization the bone-marrow culture was reported positive for tubercle bacilli. The patient continued to improve and to gain weight and was discharged to a sanatorium.

DISCUSSION

As illustrated in this case, liver biopsy may offer a practical method for confirming a diagnosis of miliary tuberculosis when other methods fail. The diagnosis was strongly suspected in this patient but the chest x-ray films were equivocal and the usual measures for immediate bacteriologic substantiation were unsuccessful. Even though streptomycin had been started in this case, punch biopsy was able to establish the diagnosis.

It should be emphasized that preliminary cultures and sputum examinations should first be carried out

intensively. It is our opinion that if the diagnosis of miliary tuberculosis is strongly suspected but cannot be immediately confirmed, streptomycin therapy should be started and liver biopsy considered for early confirmation of the diagnosis. A conclusive diagnosis early in the course of the disease would be helpful since one could then concentrate all effort on the proper treatment of the tuberculosis without subjecting the patient to other diagnostic tests and therapeutic trials in an attempt to eliminate other diagnoses. The initiation of streptomycin therapy before or after performance of the liver biopsy should minimize the risk of further spreading of the disease. It seems, however, illogical to place much emphasis on the hazard of further complicating the disease in this way, since widespread hematogenous diffusion of the bacteria to practically all organs has already occurred.

With the correct diagnosis of miliary tuberculosis quickly and easily established by punch liver biopsy, treatment can be instituted with less delay, and a better prognosis can thus be made possible.

SUMMARY

Punch liver biopsy is offered as a relatively simple, safe and practical method for the diagnosis of miliary tuberculosis when other procedures fail. A case is presented to illustrate its value.

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*We are indebted to the Pathology Department, University of Virginia Hospital for the histopathological interpretations of the biopsy specimens.

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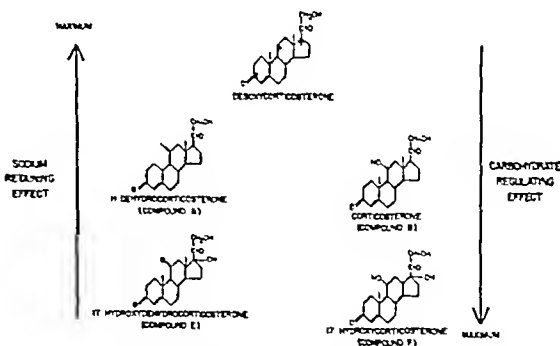


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Examples of the "carbohydrate-regulating" adrenal cortical steroids or "S" hormone are the 11-oxysteroids, Kendall's Compounds A⁴ (11-dehydrocorticosterone) and B (Corticosterone) and the much more active 11,17-oxysteroids, Kendall's Compounds E⁵ (17-hydroxy-11-dehydrocorticosterone) and F (17-hydroxycorticosterone), demonstrated in Figure 1. The effects on lymphoid tissue and eosinophils are exerted only by the 11,17-oxysteroids. In all but electrolyte effects, the latter substances are superior to the 11-oxysteroids and to 11-desoxycorticosterone. Although the salt-retaining effect of the 11,17-oxysteroids is approximately one thirtieth that of 11-desoxycorticosterone, adequate salt retention may be obtained by the use of relatively large quantities of these substances. It is therefore possible, with Compounds E and F, to maintain a satisfactory electrolyte balance in Addison's disease if adequate quantities of either of these hormones are administered. It appears that Compounds E and F may compete with 11-desoxycorticosterone in its action on electrolyte regulation. Thus, in the presence of excessive sodium retention induced by desoxycorticosterone acetate, treatment with large doses of Compound E may result, not in further sodium retention, but in increased sodium excretion.

One may achieve an approximate measure of the amount of "carbohydrate-regulating" factors secreted by following the urinary excretion of 11-oxysteroids or "cortin-like" substances,⁶ more correctly called "neutral reducing steroids", more simply, by noting a fall in the level of the circulating eosinophils referable to a rise in the circulating 11, 17-oxysteroids, or by observing the rise in the urinary uric acid-creatinine ratio, which follows an increased blood level of 11-and 11,17-oxysteroids.³ Recent evidence suggests that the adrenal cortex contains predominantly Compound F.⁷

Androgenic and Anabolic Effect of Adrenal Androgens

The third group of adrenal steroids are those referred to as the adrenal androgens or "N" hormone. It is assumed that these substances exert an effect similar to that of the testicular androgens, which consists of masculinization, with retention of nitrogen, phosphorus, potassium, sodium and chloride.⁸ This effect has been characterized as the androgenic or anabolic hormone effect. In the female it is evident that nearly all androgenic effect is derived from the adrenal cortical androgens, whereas in the male, the adrenal androgens appear to account for only two thirds of the androgenic substances, the remainder being derived from the testes. Adrenal androgens are related in structure to testosterone, but carry an oxygen group in position 11 (adrenosterone).

The secretion of androgenic substances or the administration of such steroids is evidenced by a

relatively small rise in urinary 17-ketosteroids, their excretory product.

PRACTICAL CONSIDERATIONS IN ADRENAL HORMONE THERAPY

Two groups of adrenal cortical hormone preparations are available commercially at the present time* whole adrenal cortical extracts derived from beef or hog adrenal glands and synthetic desoxycorticosterone acetate.

In cases of adrenal insufficiency the salt-retaining factors are easily substituted for by the administration of synthetic desoxycorticosterone acetate (DCA) in the form of a solution in oil (5 mg per cubic centimeter), a macrosuspension in various solvents, or in the form of subcutaneously implanted tablets or pellets weighing 125 mg or 75 mg each. Such pellets give off 0.5 and 0.3 mg, respectively, of DCA daily. These substances are ineffective in the therapy of rheumatic diseases.

Substitution therapy with "carbohydrate-regulating" factors has in the past been possible by the administration of whole extracts of beef or hog adrenal glands. Such commercial extracts contain relatively small quantities of the known steroid hormones. Aqueous whole adrenal extracts are about one tenth as potent as Lipo-adrenal Cortex (Upjohn), a concentrate of hog adrenal gland in oil, each cubic centimeter of which is equivalent to 2 mg of Compound E. In the treatment of diseases such as rheumatoid arthritis, very large quantities of whole adrenal extract will obviously be required to induce an effect comparable to that obtained from 50 to 100 mg of Compound E daily. By 1950 Compound E acetate should be available as a crystalline suspension in saline solution. Compound F, which has not been synthesized, is derived from hog adrenal glands. Doses of the same order of magnitude as Compound E acetate will probably be required in the treatment of rheumatoid arthritis. However, because of the greater solubility of Compound F, it will be necessary to increase the frequency of administration, as compared with Compound E acetate.

PITUITARY ADRENOCORTICOTROPHIC HORMONE (ACTH)

Since purified pituitary adrenocorticotrophic hormone has become available in quantities adequate for clinical investigation, it has been possible to study the effect of administering this trophic substance on the secretion of adrenal steroids in man.^{9, 10}

*Whole adrenal cortical extracts derived from beef adrenal glands in aqueous solution for intramuscular or intravenous use assayed biologically in 10-cc and 50-cc vials (for example, Adrenal Cortex Extract, Upjohn Company; Adrenal Cortex Extract, Wilson Laboratories and Eschatin Parke Davis) and from hog adrenal glands in sesame oil for intramuscular use assayed against crystalline adrenal steroids in 5-cc vials (Lipo-adrenal Cortex, Upjohn Company). —Oral preparations of adrenal cortical extract are available but relatively ineffective in the doses employed. Desoxycorticosterone acetate (DCA) of synthetic source in oil for intramuscular use in 10-cc vials (Cortate, Schering Corporation; Doxa, Hoffmann-La Roche Incorporated and Percorten, Ciba Pharmaceutical Products Incorporated). Other DCA preparations include a water soluble glucoside pellets for subcutaneous implantation, macrocrystalline suspensions and sublingual tablets and solutions.

effectiveness as an adrenal cortical stimulator since endogenous ACTH production is inhibited by a rising titer of adrenal cortical steroids. This inherent disadvantage will be found with any substance that stimulates pituitary ACTH production.

STIMULATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL-CORTICAL SYSTEM BY STRESS

Anterior hypothalamic centers have recently been shown to form an essential link in the activation of pituitary ACTH secretion following conditions of stress, as well as epinephrine administration.¹⁶ Upon nervous stimulation or contact with circulating epinephrine, a humoral substance appears to be secreted by cells of the anterior hypothalamus, which stimulates ACTH secretion.

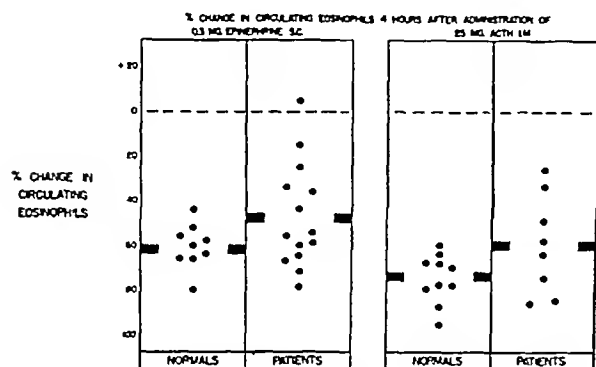


FIGURE 4 *Epinephrine and ACTH Tests in Rheumatoid Arthritis*

Through this neurohumoral system, the adrenal cortex may be activated to secrete 11,17-oxysteroids by a variety of nonspecific stresses and emotional factors (Fig 3).

Depression of circulating eosinophils has been demonstrated in a variety of moderate stresses, but the extent to which adrenal cortical activation may be accomplished by such nonspecific means awaits further investigation. It appears that the stimulatory effect upon the central nervous system of such noxious stimuli is the basis of pituitary ACTH activation. Whereas epinephrine is a good eosinolytic agent, nor-epinephrine is practically devoid of such action and is characterized pharmacologically by the near absence of any central-nervous-system stimulatory effect as compared to epinephrine.

Adrenal cortical reserve was measured by means of four-hour and forty-eight-hour ACTH tests, or both, in 22 patients with rheumatoid arthritis.¹⁷ The four-hour ACTH test using the intramuscular injection of 25 mg of ACTH and its effect on the circulating eosinophils four hours later was done on 10 patients, 8 of whom showed normal or low normal response (Fig 4). One patient who did not respond subsequently proved to be refractory to

therapy with ACTH as well. This essentially normal response in all but 1 of the group suggests that the available reserve of the adrenal cortex was not noticeably impaired by the rheumatic state. This concept was confirmed by the results of the forty-eight-hour tests, which in most cases were a continuation of the four-hour tests and were carried out using 10 mg of ACTH every six hours. All the known functions of the adrenal cortex were stimulated in all but 1 of the 10 patients.

The epinephrine test, which consists of the administration of 0.3 mg of epinephrine subcutaneously and determination of the fall in eosinophils at the end of four hours, was carried out on 14 patients with rheumatoid arthritis. The average fall of 50 per cent was slightly less than that in a similar group of normal subjects, who showed a mean 64 per cent fall (Fig 4). However, the spread of the results in the tests on patients with rheumatoid arthritis was considerably greater than that in the normal control group. Several of the patients who failed to respond normally to epinephrine re-

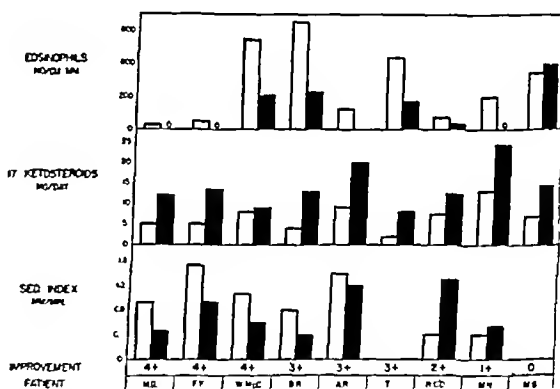


FIGURE 5 *Changes Following Forty-Eight Hours of ACTH Administration in Rheumatoid Arthritis*

sponded well to ACTH. Such a dissociation may be fortuitous or else suggests a possible deficiency in the hypothalamic-pituitary link in adrenal cortical activation (Fig 3).

EFFECT OF ACTH THERAPY ON RHEUMATOID ARTHRITIS

After the discovery by Hench, Kendall, Slocumb and Polley¹⁸ of the Mayo Clinic, that Compound E, given in large doses (100 mg per day), is effective in the treatment of rheumatoid arthritis, studies were made on the effect of the prolonged administration of ACTH to patients with rheumatoid arthritis. Ten patients were treated for from two to fourteen days with 40 mg of ACTH per day, given in divided doses of 10 mg every six hours. Of the patients treated, 5 were males and 5 females, varying in age from twenty-five to sixty-one years, the arthritis

was severe or moderately severe in 9 cases and mild in 1 case, and the duration of the disease varied from three months to twenty-eight years. In every case—that is, 9—in which the adrenal cortex responded improvement occurred. Two patients were treated for two weeks, and 8 for forty-eight hours. Within twelve to twenty-four hours of the initial administration of ACTH, clinical improvement was observed, in every way similar to that reported by the Mayo Clinic group who used 100 mg of synthetic Compound E daily.¹² The most characteristic immediate change was loss of stiffness in the joints. This was followed by improvement

in the joints, a rise in sedimentation rate and a loss of the euphoria.

Milder cases of rheumatoid arthritis show a somewhat more lasting effect after ACTH therapy, although the majority of cases return toward, but do not reach their status before treatment.

The reversion to pre-treatment status may be minimized by withdrawal of the adrenal cortical stimulation gradually. Thus, after 10 mg of ACTH intramuscularly every six hours, the same dose was given every eight hours for a week, then every twelve hours for another week, and then once a day for a short period before being discontinued altogether.

Because of the limited quantities of synthetic Compound E and natural ACTH that are available, attempts were made to increase the degree of pituitary adrenal stimulation by less specific methods. Since epinephrine has been shown to stimulate ACTH production in man, patients with rheumatoid arthritis were given a stimulating dose of epinephrine every six hours throughout the day and night. This therapy in 2 patients with rheumatoid arthritis resulted in a very slight but definite improvement, although, again, the maximum improvement observed was far less than that which occurred with ACTH or which might have been expected

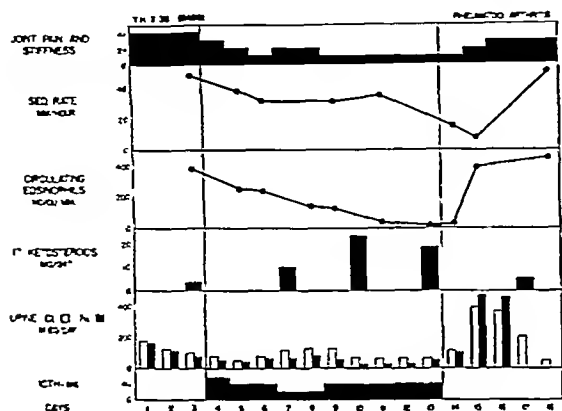


FIGURE 6 Results of Treatment with ACTH

in the patient's general sense of well-being, culminating in a euphoric state. Since this is found in patients with Addison's disease on Compound E therapy it is not related solely to decreased pain on motion.⁵ With more prolonged administration, there was increased range of motion in the joints and loss of pain. Objective evidence of improvement was found in a progressive fall in the blood sedimentation rate, often reaching normal levels after about a week. Evidence for a generally increased adrenal hormone secretion in these patients given ACTH was provided by a sustained fall in the level of circulating eosinophils, by a marked rise in 17-ketosteroid excretion and by sodium retention. Illustrative cases are shown in Figure 5 in their reaction to forty-eight hours of ACTH (95 mg). It will be noted that the patient who failed to show any improvement on forty-eight hours of ACTH did not have an eosinophil fall, although urinary 17-ketosteroids rose. The patient who showed only 1+ improvement was the single one of the group whose arthritis was initially mild. A typical case on prolonged therapy with ACTH is presented in Figure 6.

Withdrawal of ACTH therapy after two to fourteen days of treatment in 10 patients was followed in twelve to twenty-four hours by a partial return of symptoms including stiffness and pain

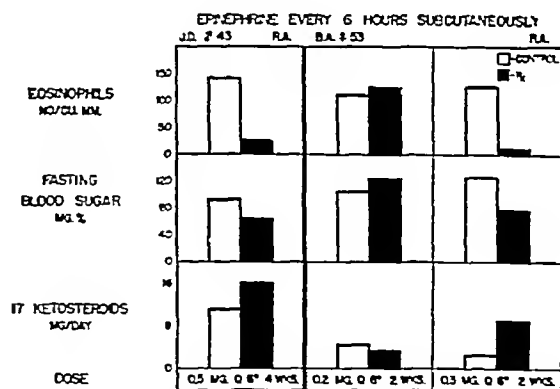


FIGURE 7 Effect of Epinephrine Treatment on Subjects with Rheumatoid Arthritis

Note the ineffectiveness of a 0.2-mg dose of epinephrine

with 100 mg of synthetic Compound E. Definite adrenal cortical activation occurred although apparently not sufficient in terms of its beneficial effect on the rheumatoid arthritic state (Fig. 7). The use of epinephrine at the termination of a course of ACTH holds promise as a means of increasing endogenous ACTH production and of buffering the sudden falling off in adrenal cortical activity, which invariably follows the discontinuance of ACTH. A number of methods of nonspecifically stimulating the pituitary to increase its ACTH output, and thereby the adrenal cortical secretion, are now being studied in patients with rheumatoid arthritis.

In addition to the studies carried out with ACTH and epinephrine, an attempt was made to improve the clinical condition of patients with rheumatoid arthritis by the administration of large quantities of adrenal cortical extract. Two cc of Lipo-adrenal Cortex (Upjohn) were given intramuscularly, every three or four hours, for one to three days, to 5 patients with rheumatoid arthritis. The total daily dose of Lipo-adrenal cortex was 12 to 15 cc. This corresponds to approximately 120 to 150 cc of aqueous whole adrenal extract. Patients with rheu-

matoid arthritis given this treatment showed very slight improvement, but the magnitude of change was in no way comparable to that observed after ACTH in our group or Compound E as described by the Mayo Clinic group. This relative ineffectiveness appears, in all probability, to be due to the fact that the total amount of extract administered contained much less than the equivalent of 100 mg of Compound E, or the quantity of Compound E or F released by the adrenal cortex upon stimulation by 40 mg of ACTH, which was given in our studies.

illustrative case in an eleven-year-old girl is shown in Figure 8. This patient was given ACTH early in her second known rheumatic attack, which was associated with subcutaneous nodules, arthritis, pericarditis and myocarditis, as suggested by a protodiastolic gallop rhythm and electrocardiographic changes. The patient was taken off acetylsalicylic acid three days before treatment with ACTH was begun. It will be noted that all the known adrenal cortical secretions appeared to be increased by ACTH, although the relative proportion by which the individual factors were augmented cannot be ascertained by current analytical methods. The posterior pituitary-like effect of Armour ACTH and the consequent retention of water lead to a rapid weight gain in most subjects being given ACTH. In a patient with incipient heart failure such a possibility is very undesirable.

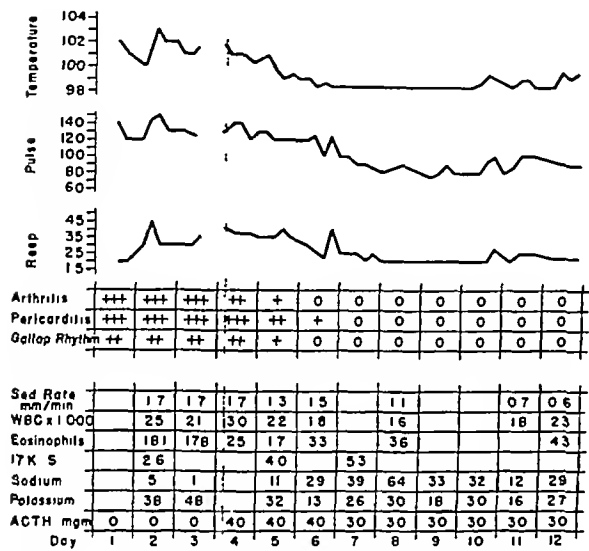


FIGURE 8 Clinical Course of a Girl with Acute Rheumatic Fever on ACTH Treatment. Sodium and potassium values refer to the daily urinary output in milliequivalents on an approximately constant diet.

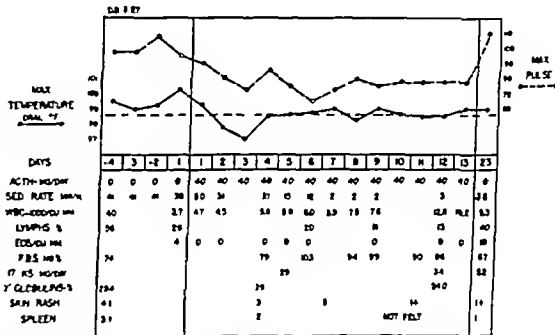


FIGURE 9 Effect of ACTH on a Patient with Disseminated Lupus Erythematosus.

matoid arthritis given this treatment showed very slight improvement, but the magnitude of change was in no way comparable to that observed after ACTH in our group or Compound E as described by the Mayo Clinic group. This relative ineffectiveness appears, in all probability, to be due to the fact that the total amount of extract administered contained much less than the equivalent of 100 mg of Compound E, or the quantity of Compound E or F released by the adrenal cortex upon stimulation by 40 mg of ACTH, which was given in our studies.

EFFECT OF ACTH ADMINISTRATION ON RHEUMATIC FEVER

The response to ACTH in patients with acute rheumatic fever is more striking than that obtained in patients with rheumatoid arthritis, in whom previous joint deformities persist in spite of ACTH-induced improvement. To date, 3 cases of acute rheumatic fever have been treated for periods varying from eight to fourteen days, with 10 mg of ACTH given intramuscularly every six hours. An

However, in the limited number of cases treated and with the dose of ACTH employed, it was found that the improvement in cardiac efficiency, with its beneficial effect on renal circulation, led to an increased urinary volume, rather than to water retention during a period of a week. The over-all benefits were identical with those obtained with Compound E acetate.¹⁹

EFFECT OF ACTH ADMINISTRATION ON DISSEMINATED LUPUS ERYTHEMATOSUS

Three patients with acute disseminated lupus erythematosus showed marked clinical improvement, with rapid disappearance of the typical butterfly rash, when given 10 mg of ACTH intramuscularly every six hours. A representative case is shown in Figure 9. The low initial eosinophil count, also found in another case, is a consequence of bone-marrow hypoplasia with normal adrenal cortical function, rather than a sign of greatly increased adrenal cortical activity as in Cushing's syndrome, in which a marked eosinopenia is diagnostic.³ It should be noted that the gamma globulins, normally 12 to 14 per cent of the total protein, did not fall

below 20 per cent during the course of ACTH therapy, and yet the sedimentation rate was decreased and the patient was clinically improved.* It is also of interest that the initial, striking clinical improvement was obtained before any change in the circulating gamma globulins. Again, all major adrenal cortical functions appeared activated. Forty milligrams of ACTH was given daily for thirteen days, followed by 20 mg daily for four days. Five days after discontinuation of ACTH therapy, the characteristic leukopenia, elevated sedimentation rate and enlarged, tender spleen returned. In spite of this, the patient was still feeling well, and the rash had not reappeared. The treatment had thus led to striking temporary improvement, which left the patient in a better clinical state but did not lead to a cure. Two subsequent ACTH courses following partial regression in this patient showed beneficial effects lasting up to six weeks.

EFFECT OF ACTH ADMINISTRATION ON GOUTY ARTHRITIS

In a study of the effect of ACTH on patients with gouty arthritis, it was found that treatment with the hormone caused a large increase in urinary uric acid excretion, with a concomitant fall in serum uric acid levels. The clinical improvement was striking and rapid. This improvement was characterized by increased joint mobility, decreased pain and softening of tophi. Although the rise in uric acid excretion was no greater than that achieved

DISCUSSION

Rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis may be viewed as related mesenchymal diseases, characterized by a nonspecific inflammatory reaction, presumably brought on by a peculiar susceptibility of the host to certain bacterial or tissue products.²² Such pathologic states are apparently favorably altered by a sudden increase in the titer of circulating 11, 17-oxysteroids or related compounds of adrenal origin. With a sudden increase in the level of these steroids, the progress of the inflammatory reaction in heart, vessels and synovia is temporarily arrested. The majority of patients with these diseases seem to possess normal adrenal cortical reserve function, but appear incapable of increasing the activity of their adrenal cortex spontaneously. Is such an activation an essential part of the normal defense mechanism? If so, is it absent in those afflicted with mesenchymal disease? Or is the massive activation of adrenal cortical hormone production by ACTH merely a therapeutic implement acting favorably upon the patient's reaction pattern to the disease directly or by neutralizing some biologic antagonist? Evidence in support of this concept is the fact that 100 mg of Compound E is needed to alter significantly the course of rheumatic diseases, whereas patients with complete adrenal insufficiency may be maintained with 10 to 20 mg daily. Effective therapy is only attained when the level of hormone is increased, to supernormal levels.

Obviously, ACTH therapy will only be effective in patients in whom a normal adrenal cortical response is obtained. A marked decrease in circulating eosinophils following ACTH therapy is a valuable indication of increased secretion of 11, 17-oxysteroids, which appear specific in their ability to depress circulating eosinophils¹⁷ and lase lymphoid tissue and which, to date, are the only type of steroid that has been shown to exert a beneficial effect in rheumatic disease.¹⁸ Since they are synthesized from bile acids, the supply of these steroids will always be limited, therefore, a search for 17-oxysteroids derived from cholesterol or plant sterols and their trial in the rheumatic state is of great practical importance. ACTH, too, is limited by the number of pituitary glands available at any one time, thus, the search for effective nonspecific pituitary-adrenal stimulants must be continued.

The mode of action of 11, 17-oxysteroids in these diseases is unknown. Improvement is observed in most patients within four to six hours. The blood sedimentation rate usually falls within forty-eight hours after treatment is begun, but the maximal change may not occur for ten to fourteen days. The initial changes that occur, such as loss of stiffness and increased capacity to move joints without pain suggest a decrease in some "stiffness factor" and an immediate reduction in the chronic inflam-

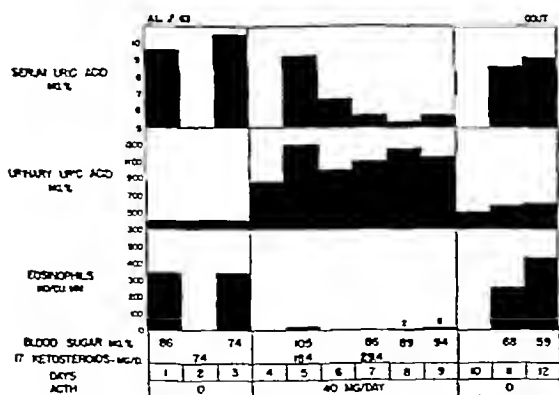


FIGURE 10 Effect of ACTH on Severe Gout

by the administration of 5 gm of acetyl salicylic acid per day,²⁰ the over-all clinical improvement was much more marked with ACTH administration. Upon withdrawal of ACTH, a mild gouty attack occurred after two days. This phenomenon has been reported by Hellman.²¹ An illustrative case is shown in Figure 10.

*The electrophoretic analyses were carried out by Dr. W. F. Leve and Dr. J. McLean of Harvard Medical School.

matory reaction. A possible cause of these changes is the effect of the hormone on tissue permeability.²³ The singular specificity of adrenal steroids in their action on rheumatic diseases is suggested by the prompt response to Compound E and the ineffectiveness of desoxycorticosterone and dehydrocorticosterone acetate. Excessive DCA treatment in patients with Addison's disease is often associated with increased stiffness of the joints or arthralgia, or both.²⁴ It is of interest that Selye²⁵ has been able to accumulate a large amount of experimental evidence suggesting that arthritis is induced in rats by the administration of excessive amounts of desoxycorticosterone, a finding recently confirmed in man.²⁶

The improvement in gout brought on by ACTH is apparently not due to increased renal uric acid clearance alone, but must also involve some direct effect on the joint tissue. Even though the effect of salicylates on the uric acid excretion is greater, the clinical improvement noted is far less than that with ACTH.

The dangers of continued ACTH or Compound E acetate treatment are principally the undesirable side-effects associated with a long-continued, high level of adrenal steroids. With chronic ACTH administration, one must be concerned with the possibility of persistent adrenal hyperplasia. Cushing's syndrome has been reported during the prolonged administration of Compound E.¹⁷ On 40 mg of ACTH per day this danger is minimal, and yet adequate adrenal cortical activation is achieved. With higher doses Cushing's syndrome is occasionally produced by ACTH as well. In all cases studied thus far on ACTH therapy there has been a rapid return of adrenal function to normal or subnormal levels. The pituitary ACTH mechanism is suppressed by exogenous ACTH and the adrenal cortex is stimulated, whereas with Compound E both the adrenal cortex and the anterior pituitary gland may become atrophic. Thus, withdrawal of Compound E therapy leads to a more acute, temporary adrenal cortical deficiency than the withdrawal of ACTH therapy. To minimize this sudden reduction in adrenal cortical activity, it appears desirable to administer ACTH for twenty-four to forty-eight hours after the withdrawal of Compound E therapy.

The beneficial effect of 11,17-oxysteroid therapy in the rheumatic diseases marks a great advance in therapy. Adrenal cortical hormone therapy does not, however, appear to affect the fundamental cause of the inflammatory changes that characterize these diseases. The use of adrenal cortical steroids or adrenal cortical stimulants will do much to further fundamental research in the field of rheumatic diseases. Their exact value as therapeutic agents remains to be worked out by long-continued therapy.

SUMMARY

The major metabolic changes induced in man by adrenal cortical steroids are described. The remarkable observations of Hench, Kendall, Slocumb and Polley on the effect of Compound E therapy in patients with rheumatoid arthritis have been extended by the use of pituitary adrenocorticotrophic hormone (ACTH). The status of the adrenal cortical function was ascertained and found to be essentially normal in 16 of 21 patients with rheumatoid arthritis. There appears to be a wide variation in the state of adrenal cortical function from patient to patient, without apparent correlation with the severity or manifestations of the disease. In 9 patients with rheumatoid arthritis in whom pituitary adrenocorticotrophic hormone was capable of stimulating the adrenal cortex to increased activity, there was striking clinical improvement and a reversal of abnormal laboratory findings. Three patients with rheumatic fever and 3 with disseminated lupus erythematosus were similarly improved by ACTH therapy, as was 1 case of gout.

With the present inadequate supply of synthetic Compound E acetate and pituitary ACTH, non-specific methods for stimulating an intact pituitary-adrenal system and naturally occurring adrenal cortical extract have been tried with little success in the treatment of rheumatic diseases.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 35401

PRESENTATION OF CASE

A five-year-old boy was admitted to the hospital because of a chronic cough.

He had been seen in the Children's Clinic one year prior to admission, when his mother stated that several months before, the patient had a severe cold, which seemed to hang on longer than normal. This cleared after several weeks but was followed by a persistent cough productive of a small amount of sputum of unknown character. Otherwise the patient was active and well.

The past history was noncontributory. A sister, ten years old, had had tuberculosis at the age of two and a half years, apparently as a result of contact with a grandmother, who died of this disease two years before the patient was brought to the clinic. It was stated, however, that the patient himself had never been brought in contact with the grandmother.

Physical examination at the time of the clinic visit showed a well developed and well nourished boy. The chest was clear to percussion, but wheezes, groans and coarse breath sounds were heard over the right side posteriorly. The rest of the physical examination was negative.

A roentgenogram of the chest showed collapse of the lateral portion of the right middle lobe, with emphysema of the medial portion (Fig 1). There was no evidence of mediastinal adenopathy.

Six weeks later the patient returned for bronchoscopy. The middle-lobe orifice was completely occluded by what looked like soft inflammatory tissue. There was reddening of the bronchus in this area. A biopsy taken at this time was sub-



FIGURE 1

sequently reported as showing chronic inflammation. Subsequent appointments were not kept, and the patient was not seen again until his present admission.

At this time the chest was clear and the general physical examination was negative except for a few small, shotty lymph nodes in the axillary and inguinal regions bilaterally.

Examination of the urine was negative. The hemoglobin was 12.4 gm and the white-cell count 11,000, with 47 per cent neutrophils, 46 per cent lymphocytes, 2 per cent monocytes, 4 per cent eosinophils and 1 per cent basophils.

A second roentgenogram of the chest showed continued evidence of involvement of the right

middle lobe, although the degree of atelectasis appeared less marked than on the previous examination one year before

On the fifth hospital day an operation was performed

DIFFERENTIAL DIAGNOSIS

DR WILLIAM BERENBERG We have here the story of a five-year-old boy whose disease started when he was three and a half years old. During all this time his general health remained excellent despite a severe, persistent cough. At the time of his first examination all the physical signs were suggestive of some obstructive phenomenon in the bronchus, and this impression was corroborated by radiologic examination as well as bronchoscopy. May we see the chest films now?

DR STANLEY M. WYMAN These films, which were taken over a three-month period, show very sharply defined, apparently segmental atelectasis in the right middle lobe, best demonstrated in the lateral view. The bronchi, as seen in these films, do not appear remarkable.

The second set of films, three months later, demonstrates definite clearing of the process. Films taken twelve days subsequently again show accentuation of the atelectasis and consolidation. This left anterior oblique film taken at the time of the original examination shows the right main bronchus, but unfortunately one cannot follow it down to the lower-lobe branches well.

DR BERENBERG Do you see any evidence of adenopathy?

DR WYMAN No.

DR BERENBERG At least there is no massive enlargement.

DR WYMAN There may well be small nodes, but I am not much impressed by them. I think that is a dubious question to settle in many cases.

DR BERENBERG These films do not add much to what we have already been told. We are thus faced with the question of determining the cause of this bronchial obstruction.

The likelihood of intrabronchial or pulmonary tumor is remote at this age. This benign course, negative biopsy, age and chest film make me believe that we need mention tumor only to exclude it.

The possibility of some congenital anomaly must be considered. The commonest malformations in this region are congenital stenosis and absence of cartilaginous rings. However, we lack the evidence of narrowing of the lumen necessary to consider this possibility seriously. Most patients with an anomaly of this type would not have remained asymptomatic for three and a half years. It would be difficult to explain the mass of soft inflammatory tissue occluding the middle-lobe orifice on this basis.

As one listens to the story, this case appears on the face of it to be a typical example of progressive

bronchiectasis in a five-year-old boy following a respiratory infection that resulted in persistent pulmonic collapse. He may very well have had unrecognized pneumonia with persistent atelectasis and progressive bronchiectasis in the involved segments. The history and physical findings are both in keeping with this diagnosis. The type and duration of cough are typical. The observation that this child was well developed and well nourished is not surprising, since we see very few children at this age with bronchiectasis who are not well above the tenth percentile for weight. Most of these children look and act well.

We are told that the middle-lobe orifice, on bronchoscopy, was completely occluded by soft inflammatory tissue. I have not seen this occur in children with post-pneumonic bronchiectasis. We have seen plugging of course, but the plugging in bronchiectasis results from the accumulation of secretions, from inspissation or occasionally from a blood coagulum, which may fill or occlude a bronchial lumen. It therefore seems to me necessary to postulate another mechanism in addition to the bronchiectasis to explain the material found at bronchoscopy. There is no mention of a specific change in the microscopical section of the biopsied material. We must assume that it probably did not exist and that what is grossly described was just inflammatory tissue. It is my opinion that this patient had bronchiectasis, although it was probably secondary to the primary cause of the bronchial occlusion.

DR BENJAMIN CASTLEMAN The report of that bronchoscopy was as follows:

Biopsy attempted. Very little if any tissue obtained.
Secretions aspirated. Some inflammatory tissue loosened,
coughed up and saved for biopsy tissue.

DR BERENBERG I think even that is unusual for ordinary post-atelectatic bronchiectasis. One may see a good deal of mucosal reddening and some inspissated material but hardly that degree of true inflammatory reaction, especially without visible hilar adenopathy on x-ray study.

In a group of cases of the so-called "middle-lobe syndrome" recently reported following pneumonia of the right lower lobe there has occurred drainage into the perihilar region sufficient to produce significant adenopathy. This may result in obstruction of the middle-lobe bronchus with or without ulceration into the bronchial lumen. This syndrome could explain the picture here, but since there are only about 20 cases reported in children, I should hesitate to make this diagnosis without a well established sequence of events.

If this patient had tuberculosis, as we are invited to believe by the family history, he probably had intrabronchial disease. Certainly, one cannot even start to discuss the question of tuberculosis without asking a number of questions. Was a tuberculin

test done? Was the aspirated material smeared for acid-fast organisms? Was this material cultured for tuberculosis? If so, what were the results?

DR CASTLEMAN Nothing is left out, intentionally, but I do not believe there was a smear

DR ALLAN M BUTLER The tuberculin test in a dilution of 1:1000 showed swelling but no redness

DR BERENBERG It seems extraordinary for swelling to occur without redness, one more often sees redness without swelling

DR BUTLER It seems extraordinary, if it was questionable, that that point was not investigated further

DR BERENBERG We have in the history the fact that this patient's sister and grandmother had tuberculosis. We have no information concerning the possible recent infectiousness of the sister. The statement that the patient had never been brought in contact with the grandmother may be misleading. Very often we obtain such a statement only to find that the patient was repeatedly shown to an infected grandparent and allowed in the same room although perhaps never held by her.

The state of well-being of this child is in keeping with intrabronchial tuberculosis at this age. Most children look the picture of health even with pulmonary lesions. Cough is not a common symptom in children with pulmonary tuberculosis as a matter of fact, but is a common symptom, of course, in intrabronchial lesions of any sort, including tuberculosis. Was fluoroscopy performed?

DR WYMAN No

DR BERENBERG It might be interesting to know if the emphysematous area changed during respiration, in order to try to decide whether the emphysema was compensatory or otherwise. This might be helpful in deciding about tuberculosis. The nature and course of this lesion are in keeping with what one would anticipate with juvenile tuberculosis. The absence of visible hilar lymph nodes and a defined pulmonary lesion are not at variance with this possibility. The presence of a few small, shotty inguinal and axillary lymph nodes is not unusual in any five-year-old child.

The interpretation of the aspiration biopsy is rather difficult. The amount of material one gets from the bronchial aspiration of the tiny lumen of a five-year-old child is limited, regardless of the lesion. If there was any nonspecific inflammatory reaction about a localized process, one would be more apt to aspirate that than the defined lesion. Most children with a tuberculous lesion of this type should be either considerably better or considerably worse in a year's time. It is not a static process and would ordinarily have cleared up or produced a bronchiogenic spread over this period. If smears had been done it would have been most helpful because the incidence of positive smears from material obtained on bronchoscopy in intrabronchial tuberculosis is higher than that from material ob-

tained in almost any other form of juvenile tuberculosis. Certainly one cannot exclude the diagnosis of tuberculosis on the information at hand, especially in the absence of a conclusively negative tuberculin test.

In any child with persistent cough, wheezing, atelectasis and evidence of bronchial obstruction, foreign body must be ruled out. In favor of foreign body is the patient's age. The commonest age is between three and five years. The fact that he had an upper respiratory infection at the onset does not bother me. In one way it is almost in keeping with this diagnosis because the incidence of aspiration is highest at the time of a common cold. I suppose that is because the child tends to have nasal obstruction and hence becomes a mouth breather. The deep inspiration following cough is conducive to the aspiration of any foreign body that the child happens to have in his mouth at that time. The clinical picture is in keeping with foreign body, and a negative bronchoscopy does not exclude the possibility of a tiny body imbedded in the wall or one lodged distal to the bronchoscopist's view. The thing that disturbs me is the fact that this disease was in the right middle lobe, which is an unusual site for a foreign body, the incidence in this lobe is only 6 to 8 per cent of all foreign bodies. The absence of a dramatic episode of coughing and choking is not unusual, especially since it might well go unnoticed in a child who then had a cold and cough. Nothing is mentioned of possible dental caries or preceding tonsillectomy. These are only two of many possible sources of aspiration to be considered. Putrefaction, if present, would favor the likelihood of aspiration, but its absence does not exclude it since any number of foreign bodies do not cause putrefaction.

I would favor the diagnosis of bronchiectasis secondary to the aspiration of a foreign body but am unable to exclude the possibility of tuberculosis without more evidence than that at hand. In addition this child had pulmonary atelectasis.

DR BUTLER Does Dr Sweet want to say a word?

DR RICHARD H SWEET When the patient was first seen on the Pediatric Service, the question of foreign body was considered and eliminated on the basis of bronchoscopic examination. I saw the boy at a later stage and to me it was a classic picture of involvement of the middle-lobe bronchus secondary to peribronchial lymphadenitis. We have seen a large number of cases like that. We have not always proved them to be due to tuberculosis. We all have seen the other group of which Dr Berenberg spoke, and I was surprised to hear it said that the number of reported cases was so small. We have an appreciable number here at the hospital but no one thought to report them as a group. It is interesting in this patient that one bronchial segment was collapsed and the other

emphysematous That was obvious at operation

The peribronchial lymph nodes were not enlarged but were very much involved in a marked peribronchial infiltration The artery and vein of the middle lobe were obscured by an infiltrative type of tissue, making dissection difficult and rather perilous, although we were able to isolate the vessels after much painstaking dissection, tying them independently In doing that, I discovered that one of the lymph nodes was calcified, and I then re-



FIGURE 2

marked that it was probably on a tuberculous basis The patient made a good recovery and has gone home

DR CASTLEMAN Do you see any specks that might be calcified lymph nodes?

DR WYMAN No, not even knowing the story

DR BUTLER Would you have operated if he had had positive smears for tuberculosis?

DR SWEET I would not hesitate to do so because I think he is far better off with the middle lobe out

CLINICAL DIAGNOSIS

Bronchiectasis, right middle lobe

DR BERENBERG'S DIAGNOSIS

Bronchiectasis, due to foreign body

ANATOMICAL DIAGNOSES

*Bronchial stenosis (middle lobe, lateral division)
produced by calcified tuberculous lymph nodes*
Pulmonary atelectasis, middle lobe, lateral segment

Miliary tubercles of lung

PATHOLOGICAL DISCUSSION

DR CASTLEMAN This is the entire middle lobe (Fig 2) From this specimen, one can see that one segment, which corresponds to the atelectatic portion on the x-ray film, is completely collapsed, whereas the other segment appears normal The cause of the obstruction in the collapsed segment is a small tuberculous calcified lymph node pushing against the bronchus but not eroding into the lumen In the lateral portion of the segment is a large caseous and calcified area of tuberculosis, which is, I believe, the primary focus An interesting and unexpected finding was the presence of small miliary tubercles, in both the collapsed and the aerated segments of the lobe, so that there must have been a hematogenous spread Some of these tubercles seem to be active, but others are fairly old We were unable to find any actual tuberculosis within the bronchus At the point of obstruction the mucosa seemed to be intact

DR SWEET It is purely a matter of pressure upon the bronchus from the exterior

DR CASTLEMAN Yes

CASE 35402

PRESENTATION OF CASE

A sixty-six-year-old Italian-born man entered the hospital for the first time complaining of cough and chest pain

He had enjoyed good health until four or five months before, when he experienced the onset of a hacking cough This was persistent and soon became productive of white, mucoid sputum Two months before admission he began to suffer pain over the left anterior thorax This was at first present only on severe coughing but rapidly became more severe until he was aware of pain at all times but particularly on deep breathing or with the slightest cough The pain was nonradiating in character and was unaltered by external pressure to the chest wall With the onset of chest pain he experienced increasing anorexia and weakness As his symptoms progressed his cough became more productive until he was bringing up half a cupful of white sputum daily A few weeks prior to admission he noted a change in pitch and timbre of his voice There was a weight loss of 25 pounds since the onset of the illness Hemoptysis, dyspnea, chills, fever and night sweats were specifically denied A review of the systems was otherwise

negative. No history of exposure to tuberculosis or to the various pathogenic dusts could be obtained. The patient had smoked two or three packages of cigarettes daily for thirty years but had voluntarily discontinued tobacco one month before admission.

Physical examination revealed a chronically ill man with signs of recent weight loss. There was no cyanosis or lymphadenopathy. The left pupil was larger than the right, but neurologic and ophthalmologic consultants denied the presence of a Horner syndrome. The trachea was not deviated. Dullness to percussion and diminished breath sounds were elicited over the anterior and posterior aspects of the left upper thorax. Fine rales were heard over both lung bases posteriorly. The heart was not enlarged, and there were no murmurs. There was a fullness in the right upper quadrant of the abdomen palpable three fingerbreadths below the costal margin. The spleen was not felt, and there was no abdominal tenderness. The prostate was three times the normal size, firm, regular and free of nodules. The fingers of the left hand had been amputated traumatically several years before. There was well developed clubbing of the remaining digits, with mild cyanosis. No peripheral edema was noted. There was weakness of the right lower facial nerve, but neurologic examination was otherwise negative.

The temperature was 99.2°F, the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The hemoglobin ranged from 13.0 to 11.4 gm, and the white-cell count from 41,000 to 57,500, with an average differential of 93 per cent neutrophils, 3 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. Many band-form neutrophils were seen but the morphology was not altered otherwise. A sternal-marrow aspiration contained 85 per cent myeloid cells, 12 per cent erythroid elements and 4 per cent plasma cells. The myeloid-erythroid ratio was 8:1. A shift to the left in the myeloid series was described. Urinalysis showed a specific gravity of 1.022, a ++ test for albumin and no Bence-Jones protein, and there were 2 or 3 red cells and 3 to 5 white cells per high-power field and occasional casts in the sediment. The stools were guaiac negative. The spinal-fluid protein was 54 mg per 100 cc. The cell count was negative. The serum protein was 6.83 gm per 100 cc, with an albumin of 3.19 and 2.85 gm and a globulin of 3.98 and 3.64 gm per 100 cc. The nonprotein nitrogen was 28 mg per 100 cc. The alkaline phosphatase was 12.1 units per 100 cc. The calcium was 9 mg per 100 cc. The prothrombin time was 70 per cent of normal. The sputum cultures grew out colon bacilli and *Haemophilus influenzae*. Three cytologic examinations of the sputum were negative.

The chest x-ray films showed a flame-like area of increased density extending from the left lung root, which occupied the central half of the left

chest and obscured the left border of the heart. A bone series showed no evidence of metastatic lesions, but there were moderate degenerative hypertrophic changes of the spine.

Throughout his hospital stay the patient exhibited a slowly rising temperature reaching 102°F by the eighteenth day, after which it varied between 104 and 105°F. The pulse varied between 80 and 120. Respirations were consistently elevated between 25 and 40. Large doses of penicillin and streptomycin failed to alter the febrile course. A spinal puncture revealed clear spinal fluid under normal pressure. Jugular compression on the right side failed to elevate the pressure. Bronchoscopy showed narrowing of the terminal portion of the left-lower-lobe bronchus, with incomplete fixation. No intrinsic masses were seen, and the remaining bronchi appeared unaltered.

On the eleventh hospital day it was noted that the patient's voice had become increasingly hoarse, and that his speech was thick. Slowly progressive mental deterioration occurred, and he declined rapidly following a distinctly septic course, which terminated in death on the twentieth hospital day.

DIFFERENTIAL DIAGNOSIS

DR JOHN R. GRAHAM: I should like to review this patient's history at the end of his first day in the hospital. So far, we have a five-month story in a sixty-six-year-old man, the essential points of which are chronic cough, chest pain, increasing amounts of sputum, weight loss, weakness, nausea and the development of a change in his voice. That story, in itself, certainly makes one think very strongly of carcinoma of the lung. The physical examination, which was done on entry to the hospital, was perfectly consistent with such a diagnosis. The chest findings, the mass in the right upper quadrant, and the suggestion of some cerebral lesion are all perfectly consistent with that diagnosis also.

Before going on with the rest of the story, I wonder if we may look at the x-ray pictures made on the second day.

DR STANLEY M. WYMAN: The chest examination is a film taken with a portable apparatus showing an irregular area of density in the left midlung field. It seems to radiate out peripherally, and there is a suggestion of some mottled density in the right lung. The next examination, eleven days later, is more satisfactory and better demonstrates the central area of density, which in the lateral view appears to be located anteriorly, probably in the left upper lobe. Again, one sees indefinite areas of mottled density in the right lung throughout its entire distribution. There are old fractures of several right ribs, and probably several fractures on the left as well. It is impossible to trace the bronchial tree well on these films because of respiratory motion. The last films, which were taken in a search for metastases, show no definite bone destruc-

tion but they do show rather extensive degenerative changes in keeping with the patient's age and probable occupation

DR GRAHAM There were no subsequent films of the chest?

DR WYMAN These are all, apparently, no subsequent films were taken

DR GRAHAM I paused at that point because it seemed to me so far that this history was a fairly characteristic one, and that it is only as we go on that the diagnosis becomes involved. What had seemed to me a rather straightforward story is now complicated by some atypical findings and happenings. In the first place, the blood picture is unusual—the high white-cell count with the high percentage of neutrophils is certainly an unusual finding, and one's first thought is whether there was some fundamental blood dyscrasia, intrinsically connected with the lesion in the chest. One might wonder if the patient had a form of leukemia, with a chest complication. However, I think that the blood picture and the marrow findings were really not strikingly abnormal, showing a bit of a shift to the left in the white-cell series rather than a marrow full of very young leukemic cells. It does not really fit in with the diagnosis of leukemia—certainly not leukemia in the stage in which the patient appeared. He did not have a large spleen, an important lack that militates against that diagnosis. He had no significant anemia, so often present in leukemia. I am assuming rightly or wrongly that his voice changes were intrinsically connected with the mass in the chest and were based on involvement of the recurrent laryngeal nerve. We are not told what the vocal cords showed. I think the laryngeal involvement is unusual in the course of leukemia, even if the disease involves the lung. I am therefore betting against leukemia. I am more inclined to think that the high white-cell count and the increase in neutrophils were probably an accentuated response to infection.

There is one other thing that crosses my mind. In the days when we were using more sulfonamides, we used to see an occasional patient with a very high white-cell count. I remember one here with a count of 72,000, and others up to 100,000 have been reported as a response to sulfonamides. I wonder if by any chance this man had been given such a drug before entry to the hospital.

Other things that bothered me were the increasing fever and the general septic course. They did not respond to the ordinary, apparently adequate chemotherapy. This raises the question of whether he had a disease that was nonbacterial in origin—either virus or fungus. I also wonder whether he had disease involving some center in the brain that has to do with temperature regulation. In connection with this one immediately begins to think of the possibility of a Hodgkin lesion, which we

know will cause fever and occurs as an isolated finding involving the chest occasionally. I have not seen this type of blood-picture response to Hodgkin's disease, although one has to admit that the presence of eosinophils with this high white-cell count is rather an unusual finding in a leukocytosis due to infection, consequently, Hodgkin's disease with its accompanying eosinophilia has to be considered. Against the possibility of Hodgkin's disease is the rather progressive course of the illness in the absence of an enlarged spleen, and the lack of any obvious lymphadenopathy elsewhere.

One, of course, has to think of all the other lung diseases, tuberculosis, empyema, abscess, and bronchiectasis, which do not particularly look like this in my estimation, and even some of the fungous diseases or histoplasmosis, which could possibly produce this type of picture. I see no evidence in their favor.

I am brought back to the original diagnosis of carcinoma of the lung probably arising from a small bronchus or the alveolar cells, with involvement of the recurrent laryngeal nerve from regional lymph nodes, and very likely some involvement of the brain and liver and possibly even the kidneys. Simpson* reported a collection of cases of carcinoma of the lung some years ago in which the most common metastases were to the bones, regional lymph nodes, liver, brain, kidneys and adrenal gland, various other organs being affected also, but these were the most important and in about that order. In favor of difficulty with the liver we have some laboratory findings, that are significant—the inverted albumin-globulin ratio, the high alkaline phosphatase and the slightly disordered prothrombin time. It is hard to guess about the kidneys, since there was only one urine report, which showed albumin and a few red cells. This may have been a result of metastases to the kidney or a response to what I think must have been the cause of his fever—namely, secondary infection with some organism not sensitive to the antibiotics used.

I will end up with a diagnosis of carcinoma of the lung with metastases in the liver and probably elsewhere, in addition to secondary infection, most likely arising in the area of the tumor and terminal septicemia.

We are told that he had an enlarged prostate. From the description it apparently was not a malignant lesion but simply prostatic hypertrophy.

A PHYSICIAN Was the serology reported?

DR BENJAMIN CASTLEMAN I am sure it was taken, but the report was not put in the record.

DR JAMES H. TOWNSEND I wonder if he had a large carcinomatous abscess behind an obstructed bronchus that was responsible for this high leukocytosis?

DR CASTLEMAN A straight abscess?

*Simpson, S. L. Primary carcinoma of lung. *Quart J Med* 22:413-432, 1929.

DR TOWNSEND Yes, abscess arising from the tumor

DR ANDRIES QUERIDO I should like to comment about the leukocytosis. Such an extremely high leukocytosis is usually infectious in origin, either streptococcal or staphylococcal, but in such cases eosinophils are absent. The only other condition that I know of in which it is found and in which eosinophils are present is a highly necrotizing tumor, not an abscess. The white-cell count may go as high as 50,000 or 60,000. First of all, this illustrates that it is very worth while to count the eosinophils per cubic millimeter. It is a very easy thing to do. If this patient had 500 eosinophils per cubic millimeter, I would say not abscess, but a highly necrotizing carcinoma.

A PHYSICIAN Is it not true that carcinomas, particularly those of the kidney and liver, give rise to a high white-cell count without infection?

DR CASTLEMAN Yes, increased white-cell counts occur in renal-cell carcinoma, carcinoma of the lung and primary hepatoma.

DR QUERIDO An eosinophilia in hepatoma.

DR CASTLEMAN In hepatoma it is possible to find thrombi in the hepatic veins, and even in the portal radicles, which might account for some necrosis.

CLINICAL DIAGNOSES

Carcinoma of lung
Pseudoleukemia

DR GRAHAM'S DIAGNOSES

Carcinoma of lung with metastases in liver, probably elsewhere
Secondary infection
Terminal septicemia

ANATOMICAL DIAGNOSES

Carcinoma of lung undifferentiated, upper lobe with extensive necrosis and with metastases to lungs, bronchial lymph nodes, liver, adrenal glands and brain.

Atelectasis, compression type posterior apical and superior lingular segments upper lobe of left lung

Bronchiectasis, chronic severe

Pulmonary osteoarthropathy severe

Mieloid hyperplasia of bone marrow

Atherosclerosis, coronary artery and aorta, moderate

PATHOLOGICAL DISCUSSION

DR CASTLEMAN This patient's tumor was, as seen on x-ray study and as Dr Graham predicted, in the left upper lobe and was a solid mass that extended anteriorly and, in fact, went over the midline a bit. The tumor was extremely necrotic, not a true abscess, but merely necrosis of tumor. There was only one metastatic nodule close to the tumor and several metastatic nodules throughout the other lung. The anterior and mediastinal extension of the tumor was really extension rather than metastases to regional lymph nodes. There were numerous metastases to the liver, which accounted for the high alkaline phosphatase and other impaired liver-function studies. There were metastases to both adrenal glands, but none to the kidneys. The tumor was an undifferentiated one, in places it looked almost sarcomatous, with spindle-shaped cells. Mitoses were very common, and many cells had four or five nuclei such as one sees in undifferentiated sarcoma. On the other hand, when one studied the metastases where the tumor was not as undifferentiated, the cells were unquestionably of epithelial origin so that one would call it an undifferentiated carcinoma rather than an oat-cell, adenocarcinoma or squamous-cell lesion, which are the more usual types seen.

DR GRAHAM How about the brain?

DR CASTLEMAN It measured 5 mm in diameter in the left superior frontal gyrus.

DR QUERIDO Was the kidney stained for amyloid?

DR CASTLEMAN No, but there was nothing to suggest amyloid in the routinely stained sections.

DR GRAHAM I think that the fever was explained by the process that Dr Querido has suggested. That is interesting. More attention ought to be paid, perhaps to the eosinophil count.

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An analysis of the report of the Committee on Medical Services of the Commission was presented at the annual meeting of the Massachusetts Medical Society by Professor Hugh R. Leavell of the Harvard School of Public Health and appears as the leading article in this issue of the *Journal*

When the report was first released it became immediately apparent that the federal Government was spending far too much money on medical and public-health operations, most of the expenditures being made by the Veterans Administration, the armed forces and the Federal Security Agency. The taxpayer may well be aghast at the medical bill of \$1,250,000,000, incurred in 1948, even accustomed as he has become to governmental extravagance.

The chief present weaknesses in the health services are in the medical-care program rather than in public health and research. This consists of competition between agencies for scarce personnel, wasteful construction of hospitals without over-all planning, and failure to utilize existing facilities to the best advantage. A lack of centralized responsibility for the over-all federal health plan has resulted in the competition among agencies for scarce medical and technical personnel and in hospital construction regardless of the plans or needs of other agencies or of state and local facilities. Construction costs range from \$20,000 to \$51,000 per bed, with voluntary hospital construction estimated at about \$16,000 per bed. The dollar has apparently two values — fifty cents to the average citizen, and a quarter when spent by the Government! The geographic location of Veterans Administration Hospitals has also been unwise, and the policy regarding beneficiaries of federal medical service is unclear.

The recommendations of the report specify in particular a united medical administration to have control of Veterans Administration hospitals, general, post and station hospitals of the armed forces within the continental United States, the entire Public Health Service, nonmilitary hospitals in the Canal Zone, and hospitals of the Food and Drug Administration. At its head should be "the ablest health and medical administrator obtainable," who would be appointed by the President and confirmed by the Senate.

Congressional action should define clearly those who are entitled to the benefits of Government care, and a survey should be made to determine the amount of federal assistance that is necessary for medical and health education.

Research, preventive medicine and public health—all of which are factors in the prevention of disease—should be given high priority. The best way of lowering the costs of medical care is to decrease the need for it.

Although the Commission was divided on this point, the consensus of opinion was in favor of an independent health agency at the present time, rather than one that would combine health, education and security. Such a combination, however, might be eventually desirable.

THE ADRENAL GLAND AND THE RHEUMATIC STATE

THE discovery by Hench and his collaborators^{1, 2} of the remarkably beneficial effect of a particular adrenocortical steroid (compound E or Cortisone) on the course of rheumatoid arthritis and rheumatic fever has been amply confirmed and must be classified as one of the significant achievements of modern medicine. Elsewhere in this issue of the *Journal* Thorn and his associates show that stimulation by anterior pituitary adrenocorticotrophic hormone (ACTH or ACTARMOUR) is equally effective by inducing the secretion of substances similar to compound E by the patient's own adrenal glands. The striking improvement in symptomatology and the establishment of an almost euphoric state in patients with rheumatoid arthritis or rheumatic fever far surpasses the effects of any of the conventional drugs now employed. It is already apparent, however, that withdrawal of therapy may precipitate recurrence of symptoms, particularly in patients with rheumatoid arthritis. This suggests that the primary cause of the rheumatic state is not affected by adrenal-hormone therapy, although the manifestations of the disease are completely abolished.

Studies on the state of adrenocortical function in patients who subsequently respond to treatment do not permit one to postulate *absolute* adrenocortical insufficiency as a prerequisite to the development of the rheumatic state. In fact, rheumatoid arthritis is rarely seen among untreated patients with Addison's disease. The very large dose of Cortisone (100 mg daily) required to initiate a therapeutic response may lead to the development of Cushing's

syndrome, a manifestation of adrenocortical overactivity, when the drug is administered for periods exceeding two weeks. The effective therapeutic dose thus exceeds the quantity produced by the adrenal glands under normal circumstances. This suggests that the effect in rheumatoid arthritis represents a pharmacologic action of the hormone. The presence of factors inhibiting the normal physiologic action of Cortisone in patients with rheumatic disease must also be considered.

The rapid and dramatic improvement that follows therapy forms a unique opportunity to investigate the pathogenesis of these hitherto baffling disorders. The rapidity with which initial improvement is noticed (often within six hours of the injection) raises interesting speculation concerning the mechanism by which the course of such persistent and chronic disorders as rheumatoid arthritis, disseminated lupus and rheumatic fever is modified.

It is apparent that, in contrast to Cortisone, improvement in these disorders with ACTH therapy presupposes the capacity of the patient's own adrenal glands to produce large quantities of hormone for prolonged periods. It is to be anticipated that under certain circumstances adrenocortical reserve might be low, and ACTH therapy hence would be relatively ineffective. With both drugs undesirable side effects resulting from excessive adrenal-hormone therapy must be anticipated. The adrenal glands of patients treated with Cortisone will presumably undergo compensatory atrophy during the period of therapy, whereas with ACTH treatment there will be marked hypertrophy and hyperplasia. With both drugs the function of the anterior pituitary body, at least in the production of ACTH, will be depressed. It appears that the adrenal gland and pituitary body return to their normal state within a few days of the discontinuance of therapy.

To date Cortisone and the closely related 17-hydroxy-corticosterone or compound F have proved to be by far the most effective antirheumatic agents, making them practically specific. Cortisone, being derived from bile acids by a twenty-four-step chemical procedure, is limited in amount and of necessity very expensive. An active search for other sources of more immediate precursors of Cortisone has led

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Although the Commission was divided on this point, the consensus of opinion was in favor of an independent health agency at the present time, rather than one that would combine health, education and security. Such a combination, however, might be eventually desirable.

THE ADRENAL GLAND AND THE RHEUMATIC STATE

THE discovery by Hench and his collaborators^{1, 2} of the remarkably beneficial effect of a particular adrenocortical steroid (compound E or Cortisone) on the course of rheumatoid arthritis and rheumatic fever has been amply confirmed and must be classified as one of the significant achievements of modern medicine. Elsewhere in this issue of the *Journal* Thorn and his associates show that stimulation by anterior pituitary adrenocorticotrophic hormone (ACTH or ACTARMOUR) is equally effective by inducing the secretion of substances similar to compound E by the patient's own adrenal glands. The striking improvement in symptomatology and the establishment of an almost euphoric state in patients with rheumatoid arthritis or rheumatic fever far surpasses the effects of any of the conventional drugs now employed. It is already apparent, however, that withdrawal of therapy may precipitate recurrence of symptoms, particularly in patients with rheumatoid arthritis. This suggests that the primary cause of the rheumatic state is not affected by adrenal-hormone therapy, although the manifestations of the disease are completely abolished.

Studies on the state of adrenocortical function in patients who subsequently respond to treatment do not permit one to postulate *absolute* adrenocortical insufficiency as a prerequisite to the development of the rheumatic state. In fact, rheumatoid arthritis is rarely seen among untreated patients with Addison's disease. The very large dose of Cortisone (100 mg daily) required to initiate a therapeutic response may lead to the development of Cushing's

syndrome, a manifestation of adrenocortical overactivity, when the drug is administered for periods exceeding two weeks. The effective therapeutic dose thus exceeds the quantity produced by the adrenal glands under normal circumstances. This suggests that the effect in rheumatoid arthritis represents a pharmacologic action of the hormone. The presence of factors inhibiting the normal physiologic action of Cortisone in patients with rheumatic disease must also be considered.

The rapid and dramatic improvement that follows therapy forms a unique opportunity to investigate the pathogenesis of these hitherto baffling disorders. The rapidity with which initial improvement is noticed (often within six hours of the injection) raises interesting speculation concerning the mechanism by which the course of such persistent and chronic disorders as rheumatoid arthritis, disseminated lupus and rheumatic fever is modified.

It is apparent that, in contrast to Cortisone, improvement in these disorders with ACTH therapy presupposes the capacity of the patient's own adrenal glands to produce large quantities of hormone for prolonged periods. It is to be anticipated that under certain circumstances adrenocortical reserve might be low, and ACTH therapy hence would be relatively ineffective. With both drugs undesirable side effects resulting from excessive adrenal-hormone therapy must be anticipated. The adrenal glands of patients treated with Cortisone will presumably undergo compensatory atrophy during the period of therapy, whereas with ACTH treatment there will be marked hypertrophy and hyperplasia. With both drugs the function of the anterior pituitary body, at least in the production of ACTH, will be depressed. It appears that the adrenal gland and pituitary body return to their normal state within a few days of the discontinuance of therapy.

To date Cortisone and the closely related 17-hydroxy-corticosterone or compound F have proved to be by far the most effective antirheumatic agents, making them practically specific. Cortisone, being derived from bile acids by a twenty-four-step chemical procedure, is limited in amount and of necessity very expensive. An active search for other sources of more immediate precursors of Cortisone has led

to their discovery in an African strophanthus plant and a Mexican yam. ACTH is, at present, derived from the pituitary body of domestic animals, the hog in particular. Some 4000 hogs will yield enough ACTH to treat one patient for twenty days. In the present difficulty with totally inadequate supplies of Cortisone and ACTH for large-scale therapeutic use, the producers of these substances have adopted specific plans for the equitable distribution of the material.

Cortisone (Merck) is sold to competent investigators only after their specific requests to and acceptance by a committee appointed by the National Academy of Science. The requirements of the committee are such that the investigators must have adequate facilities for properly studying the over-all metabolic effects, mode of action and clinical influence of the hormone in various disease states. ACTH is distributed to competent investigators for the same purpose by the Armour Laboratories.

In the present search for other effective agents in the treatment of the so-called "collagen" diseases and in reviewing the older forms of treatment that have proved helpful in certain cases, one is constantly confronted with this question: Is the drug effective because of its specific pharmacologic action, or is it merely one of many agents capable of eliciting a nonspecific pituitary-adrenal response and thereby of increasing the level of circulating adrenocortical steroids temporarily? The studies of Selye et al.³ leave no doubt that a wide variety of stresses initiate a response that is characterized by the liberation of pituitary ACTH and secondarily adrenocortical hormone. Any agent or procedure capable of eliciting this reaction in a patient with rheumatoid arthritis must be considered potentially capable of initiating a profound change in the course of the disease. Unfortunately, it is usually not possible to obtain an excess of adrenal hormone for prolonged periods by nonspecific means because of the depressing effect of a high level of circulating adrenal steroids on further pituitary-ACTH production.

Although it is too early to evaluate the ultimate clinical usefulness of these drugs in the treatment of rheumatic disease, there is no doubt that investigation in this field of disease has been given a tremen-

dous stimulus. Furthermore, preliminary reports suggest that the usefulness of these hormones is not limited to the group of so-called "collagen" diseases, but that they have much more widespread value.

REFERENCES

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UNIPOLAR ELECTROCARDIOGRAPHY

ELECTROCARDIOGRAPHY is often said to be an empirical science, but it can hardly be termed static. The physician who labored long and hard to master the standard bipolar limb leads was not allowed to relax with his newly gained knowledge very long. The introduction of bipolar precordial leads into clinical practice, after much debate and in the face of considerable objection, made it necessary for him to continue to dig into the journals and newer textbooks in order to keep abreast of the field. Those who made the effort were not long in appreciating the great value of the innovation, particularly in the diagnosis of anterior myocardial infarction. As experience accumulated, the additional value of multiple precordial leads became apparent. As if this were not enough, the practice of taking bipolar leads was challenged, and the advantages to be gained by rendering one electrode indifferent were pointed out, originally by Wilson and later by Goldberger. Although some years have elapsed since Wilson introduced the technic, it has only recently begun to receive the attention it deserves.

The need for a more precise electrocardiographic method for determining relative right or left ventricular predominance has long been recognized. Inextricably bound up with the same problem is the question of how best to determine the position of the heart electrocardiographically, since, in many cases, enlargement of a ventricle greatly influences the position of the heart. With standard limb leads alone, there may be no way to differentiate changes due to alteration in the position of the heart.

and those due to a damaged myocardium Goldberger, by the use of augmented unipolar leads and by his emphasis on unipolar limb leads, has shown how unipolar electrocardiography may be the key to many problems involving changes in the position of the heart or enlargement of a ventricle, or both.

It is still too early to advocate the routine clinical use of unipolar limb leads, augmented or otherwise. Unipolar chest leads are used routinely by many electrocardiographers, and some knowledge of them is rapidly becoming essential. In the diagnosis of myocardial infarction it is doubtful that unipolar electrocardiography possesses any great advantage over bipolar methods. In anterior infarcts the standard bipolar limb leads and multiple precordial leads, either unipolar or bipolar, are likely to provide information of diagnostic value, particularly if serial studies are carried out. For the diagnosis of posterior infarcts the physician must still lean heavily on the standard bipolar limb leads. It seems likely, however, that when satisfactory standards for unipolar leads are developed and as experience grows, the technic may find a permanent place in the list of useful electrocardiographic procedures. The specific value of augmented unipolar leads is yet to be defined, but Goldberger's interpretation of unipolar limb leads should be borne in mind whenever information concerning the position of the heart is needed. The further development of unipolar electrocardiography is well worth watching by physicians interested in cardiology.

NATIONAL BIRTH STATISTICS

A RELEASE from Federal Security Administrator Oscar R. Ewing discloses that "a greater proportion of births in the United States were delivered in hospitals or institutions in 1947 than in any previous year on record."

The number of registered live births during 1947 rose to a peak of 3,699,940, with the proportion occurring in hospitals reaching a new high of 84.8 per cent.

Births attended by physicians were higher in urban than in rural areas, 98.0 per cent and 90.3 per cent respectively, and markedly higher in white (98.5 per cent) than in nonwhite (67.4 per cent).

populations. Deliveries in Connecticut, Nebraska, New Hampshire and the District of Columbia were attended by physicians in 100 per cent of the cases, although in the District of Columbia, interestingly enough, 10 per cent of the births are also listed as having been attended by midwives. In Massachusetts and Vermont 99.9 per cent of cases were attended by physicians with no midwives participating in any case. In Mississippi physicians attended 61.4 per cent of the deliveries, midwives caring for the remainder.

It will be seen by our weekly report that the cholera is no longer in the city as an epidemic. Of the 5 deaths from the disease last week, 3 were individuals just arrived from other places. Although its ravages here have been light compared with those of some other places, yet it has numbered over 600 victims during the three months of its prevalence, and has increased the mortality of the city, during some weeks, more than a hundred per cent above the weekly average.

Boston M & S J, October 3, 1849

MASSACHUSETTS MEDICAL SOCIETY



DEATHS

HARTNETT — John H. Hartnett, M.D., of Worcester, died on May 10. He was in his seventy-fourth year.

Dr. Hartnett received his degree from Tufts College Medical School in 1911. He was affiliated with Belmont Hospital and St. Vincent Hospital. He was a fellow of the American Medical Association.

His widow, a son, two daughters, a brother and three sisters survive.

LAMBERT — John H. Lambert, M.D., of Lowell, died on September 10. He was in his seventy-fourth year.

Dr. Lambert received his degree from Boston University School of Medicine in 1899. He was formerly senior-surgeon at Lowell General Hospital and consulting roentgenologist at Bedford Veterans Administration Hospital. He was a former president of Middlesex North District Medical Society and was a member of the New England Roentgen Ray Society and the American Roentgen Ray Society and a fellow of the American College of Surgeons and American Medical Association.

His widow, three daughters, two sons and nine grandchildren survive.

MASON — Robert L. Mason, M.D., of Wellesley, died on September 20. He was in his fifty-third year.

Dr. Mason received his degree from Harvard Medical School in 1922. He was formerly chief of the surgical staff at Cushing General Hospital and a member of the staff of the Lahey Clinic. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow, a son and three daughters survive.

to their discovery in an African strophanthus plant and a Mexican yam ACTH is, at present, derived from the pituitary body of domestic animals, the hog in particular. Some 4000 hogs will yield enough ACTH to treat one patient for twenty days. In the present difficulty with totally inadequate supplies of Cortisone and ACTH for large-scale therapeutic use, the producers of these substances have adopted specific plans for the equitable distribution of the material.

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consequent immunity alone is desired, however, only one specimen need be submitted

For information regarding serologic diagnosis of other virus infections, the Laboratory should be consulted directly (telephone, Jamaica 4-5440). It should be noted that none of these tests will assist in confirming diagnosis during the early acute stage. They are useful mainly in making diagnosis in retrospect. Since funds for these services are limited, physicians should send specimens of real diagnostic importance only.

UNUSUAL SEROLOGIC TESTS

It is not practical for a state laboratory to attempt to perform certain unusual tests requested by physicians infrequently and at irregular intervals. It has been the practice to forward such specimens to one of the laboratories of the United States Public Health Service.

Some of the unusual serologic tests formerly performed at the National Institutes of Health, Bethesda, Maryland, are now being done entirely at the Communicable Disease Center in Georgia. These are amebiasis, trichinosis, echinococcus and leptospirosis. These specimens should hereafter be sent to Immunology-Serology Laboratory, Communicable Disease Center, United States Public Health Service, Chamblee, Georgia.

Serologic tests for trypanosomiasis, schistosomiasis, filariasis, leishmaniasis and toxoplasmosis should still be sent to Laboratory of Tropical Diseases, National Institutes of Health, Bethesda 14 Maryland.

DISCONTINUANCE OF DISTRIBUTION OF VARIOUS DRUGS

The Massachusetts Department of Public Health has discontinued the distribution of nearsphenamine, sulfarsphenamine and sulfathiazole tablets. However, the distribution of Mapharsen and bismuth subsalicylate in oil to private physicians for the treatment of patients with syphilis will be continued.

MISCELLANY

MASSACHUSETTS ASSOCIATION OF SCHOOL PHYSICIANS

At a meeting of the interim committee of the Massachusetts Association of School Physicians, attended by Drs. Mary Moore Beatty, Antonio Milone, Anthony H. Nikiel, Alan Poole, Honoria K. Shine and Allan R. Cunningham, chairman, and held on September 11 at Hotel Sheraton, Worcester, a draft of the proposed constitution was completed.

Copies of this draft will be mailed to each of the 620 school physicians of Massachusetts, and further organization will proceed by meetings of school physicians in each of the eight health districts of the Commonwealth.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Manual of Clinical Laboratory Methods. By Opal E. Helper, Ph.D., M.D., associate professor of pathology, Northwestern University Medical School, director of the clinical laboratories, Montgomery Ward Clinics and Passavant Memorial Hospital, and consultant in clinical pathology, Children's Memorial Hospital, Chicago. With a foreword by James P. Simonds, Ph.D., M.D. Fourth edition. 4°, cloth, 387 pp. with 36 illustrations. Springfield, Illinois: Charles C. Thomas, 1949. \$8.50.

The first edition of this standard work was published originally in 1935. The soundness and popularity of the manual is attested by the need of this fourth edition. The book is intended primarily for use in the teaching of medical students and laboratory technicians, and is not designed as a textbook on clinical pathology. In most instances only one method is included for each determination, and the procedures are given in outline form so that they may be followed easily in the laboratory. There is a comprehensive index, and the book is well published. It should prove useful to the laboratory worker.

The Psychoanalytic Reader: An anthology of essential papers with critical introductions. Volume I. Edited by Robert Fliess, M.D. 8°, cloth, 392 pp. New York: International Universities Press, Incorporated, 1948. \$7.50.

This volume, the first in a projected series, comprises important contributions selected from the literature of the period beginning with 1909 and extending to date. The material is divided into five parts: clinical, theory, miscellaneous uncollected papers of Karl Abraham, and references by Freud (to six publications of other authors). The part on theory includes the articles on female and preoedipal sexuality. There should have been an index, if only of authors. The series should be in all collections on the subject.

Child Psychiatry. By Leo Kanner, M.D., associate professor of psychiatry, Johns Hopkins University School of Medicine, and director, Children's Psychiatry Service, Johns Hopkins Hospital. With prefaces by John C. Whitehorn, M.D., Henry Phipps Professor of Psychiatry, Johns Hopkins University School of Medicine, Adolf Meyer, M.D., LL.D., and Edwards A. Park, M.D. Second edition. 4°, cloth, 752 pp. Springfield, Illinois: Charles C. Thomas, 1949. \$8.50.

This standard work was published first in 1935 and reprinted four times from 1937 to 1947. In this second edition the author has completely rewritten his book, incorporating the great advances made in the subject during the past thirteen years. This second edition was published simultaneously in the United States, Great Britain and Canada, and in Spanish in Chile. The text is divided into four parts: history, basic orientation, clinical considerations, and phenomenology, again subdivided into three sections, including personality problems arising from physical illness, psychosomatic problems and problems of behavior. The material is well arranged and well written and documented throughout with references to the appropriate literature. There are indexes of authors and subjects. The printing is well done with a beautiful, large type. The book is recommended for all medical and sociologic libraries and to psychiatrists and pediatricians.

NOTICES

ANNOUNCEMENT

Dr. Francis A. Walsh announces the removal of his office to 1826 Centre Street, West Roxbury.

NOTES FROM THE MEDICAL EXAMINER

DETERMINATION OF THE BLOOD GROUPS OF DRIED BLOOD STAINS

The antigens A and B, which determine the classic blood groups, are relatively stable substances. Therefore, it is possible to determine their presence in dried blood stains and thus indirectly to determine the group of blood that produced the stain. The principle of this technic is as follows:

One allows a mixture of anti-A and anti-B reagent to react with the stain. The quantities of agglutinins in the reagent are carefully adjusted so that a stain that contains only a small amount of A, for example, will remove all the anti-A. The anti-B is similarly adjusted. These amounts are determined by preliminary tests on stains of known groups. The reaction is usually carried out with about 1 sq. cm. of material, such as stained cloth, finely cut up with scissors and mixed with the anti-A and anti-B reagent in a test tube. After this mixture has been allowed to stand overnight, preferably with occasional mixing during the interval, a drop of the liquid is taken off with a wire loop and is tested with Group A cells. A similar preparation is made with a loopful from the mixture and Group B cells. If Group A cells are agglutinated, but Group B cells are not, one may conclude that the following sequence of events took place: the anti-B in the reagent was neutralized by the B substance contained in the stain and thereby prevented from exerting further action against Group B substances so that when the supernatant was tested against Group B cells, no reaction took place. The anti-A in the liquid, on the other hand, since it met no Group A substance, was not used up and was still active in the supernatant liquid.

The volume of the reagent applied to the stain should permit an excess of two or three loopfuls; the concentration of the reagent should be such that anti-A and anti-B are approximately 1:8 of human serum of 1:64 titer.

During the test of the supernatant, which is usually carried out on a microscope slide, provision must be made to prevent evaporation. This can be done by a moist chamber or a sealed hanging-drop preparation.

The possible reactions are as follows: the stain may remove neither anti-A nor anti-B or may remove one or the other, or both. In each case the diagnosis of the blood group of the stain is shown: Group O, no agglutinin removed; Group A, anti-A removed; Group B, anti-B removed; Group AB, anti-A and anti-B removed.

In order that the highest confidence may be placed on the test it is extremely desirable that at the same time stains of known group and of similar age be tested under similar conditions. When all reagents are suitably chosen, and the tests are

properly conducted, stains no larger than 1 cm. in area may be identified. Age alone, in the absence of putrefaction, is not a serious limitation for evidence has been put forward that stains for years old have been correctly identified.

Another desirable control is to test the material away from the stain—cloth, paper or whatever it may be—to demonstrate the absence of specific or nonspecific power to remove either anti-A or anti-B agglutinin from the reagent.

It is possible to confirm a grouping by testing recent stain for the agglutinins anti-A or anti-B, or both. The finding of both in a stain thought to be Group O is a welcome confirmation. These tests are best carried out by the "crusts" technic of Lattes. However, the agglutinins deteriorate more rapidly than the agglutinogens.

WILLIAM C. BOYD, PH.D.

Professor of Immunochemistry, Boston University School of Medicine

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SEROLOGIC TESTS FOR VIRUS DISEASES

The Department has previously announced to physicians its facilities for performing a limited number of serologic tests for certain virus diseases, such as influenza A and B, mumps and lymphocytic choriomeningitis. To this list is now added tests for cold agglutinins, useful in the diagnosis of atypical pneumonia, as well as complement-fixation tests for the more common encephalitides.

Specimens should be submitted in the Department's special outfit, and accompanied by properly filled out forms entitled "Request for Serologic Tests for Certain Virus Diseases." The "agglutinations-cultures outfit" to be used (previously called the "undulant-fever outfit") and the special forms to be filled out may be obtained from local boards of health, or directly from the Massachusetts Department of Health, Bacteriological Laboratory, 281 South Street, Jamaica Plain 30.

In each suspected case, two aseptically collected 4-cc. serum specimens are required, the first taken as soon as possible after the onset of the disease, and the second ten to fourteen days later (six weeks or more after onset for neutralization tests in cases of lymphocytic choriomeningitis). If facilities for separation of serum are not available, 10 cc. of clotted blood for each specimen may be substituted if it is mailed to the laboratory at once. *Since positive diagnosis can be made only if a rise in antibody titer is demonstrated (fourfold or greater is considered significant) during the course of the illness, two specimens must be sent.* Tests for diagnosis, therefore, will be run only on paired specimens. If information regarding past mumps infection and

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HIRSCHSPRUNG'S DISEASE A NEW CONCEPT OF THE ETIOLOGY*

Operative Results in Thirty-Four Patients

ORVAL SWENSON, M.D. † HAROLD F. RHEINLANDER, M.D., ‡ AND ISRAEL DIAMOND, M.D. §

BOSTON

CONGENITAL megacolon has been recognized as a clinical entity for over a hundred years. Many reports were written on the subject before Hirschsprung¹ published his classic description of the disease in 1888. His presentation included the clinical study and autopsy findings of 2 patients with megacolon and was more complete than anything previously recorded. Subsequently, scores of papers have been written on the etiology and treatment of megacolon.

The numerous theories set forth in these publications may be divided into four categories and summarized as follows:²

The disease is due to congenital lesions in the dilated colon. Hirschsprung¹ thought that both the hypertrophy and the dilatation of the bowel were congenital. Miva⁴ believed that although the dilatation was congenital the hypertrophy was secondary and occurred after birth.

The cause is a mechanical obstruction that produces the dilated and hypertrophied colon. Marfan⁵ postulated that an elongated and looped colon could result in the clinical and pathological picture. Treves⁶ thought that the condition was due to an actual mechanical obstruction and that the dilatation and hypertrophy could be explained on this basis.

The disease may be due to infection of various types. Among the proponents of this theory were Walker and Griffiths,⁷ who suggested that chronic colitis was the beginning pathologic change initiating a chain of events that finally resulted in Hirschsprung's disease.

The condition is due to a neurogenic imbalance. Most students of the disease during the past two decades have suggested theories that postulate

some type of deficiency of nerve supply to the bowel. In 1900 Fenwick,⁸ who was the first of this group, stated that spasm of the anal sphincter resulted in dilatation of the colon. Hawkins,⁹ in 1907, labeled the disease "neuropathic dilatation and hypertrophy of the colon." He suggested that a neuromuscular defect existed in one segment of the colon, and that intestinal contents had difficulty in passing through this area. In 1926 Fraser¹⁰ wrote about malfunction of the colon associated with defective relaxation of the sphincter due to abnormalities in the involuntary nervous system. Wade and Royle,¹¹ in 1927, agreed that the disease was due to a similar mechanism caused by an overactive sympathetic nervous system; they performed lumbar sympathectomy to obviate sympathetic overstimulation. Martin and Burden,¹² in the same year, claimed that "rectosigmoid sphincterismus" due to derangement of intrinsic nerve supply caused a partial intestinal obstruction resulting in the disease. In 1930 Scott and Morton¹³ showed that spinal anesthesia produced evacuation of the colon in patients with Hirschsprung's disease. This was accepted as evidence that overactivity of the sympathetic nervous system existed.

Considerable differences of opinion also exist about treatment. The methods of therapy employed at present may be divided into three groups: attempts to control the disease by medical management, surgical treatment consisting of resection of parts or all of the dilated and hypertrophied colon, and section of the sympathetic pathways to part or all of the colon.

Medical treatment consists of special diets, laxatives and enemas, and various drugs that influence intestinal motility. Success has been reported with such drugs as Mecholyl bromide¹⁴ which tend to increase intestinal peristalsis. Equally good results have been reported with syntropan.¹⁵ These two drugs presumably have opposite effects, the former being a parasympathomimetic and the latter a

*From The Children's Hospital, Children's Medical Center, and the Departments of Surgery and Pathology, Harvard Medical School.

This investigation was supported by funds from the Grant Foundation.

†Associate in surgery, Harvard Medical School; surgeon, The Children's Hospital, Children's Medical Center.

‡Research fellow in surgery, Harvard Medical School; fellow in surgery, The Children's Hospital, Children's Medical Center.

§Assistant in pathology, Harvard Medical School; assistant pathologist, The Children's Hospital, Children's Medical Center.

LAY MEETING ON DIABETES DETECTION

A lay meeting on diabetes detection will be held in the John Hancock Hall of the new John Hancock Building in Boston on October 10. Sponsoring organizations are the New England Diabetes Association, the Committee on Diabetes of the Massachusetts Medical Society, and the American Diabetes Association.

The following outstanding investigators in the field of diabetes will speak: Dr. H. C. Hagedorn, of Copenhagen, Denmark, the discoverer of protamine insulin; Dr. Charles H. Best, winner of the Nobel Medal and co-discoverer of insulin; and Dr. Howard F. Root, of Boston.

Announcement of gifts from Denmark and Canada for the establishment of research foundations in the United States will be made at the meeting.

BOSTON CITY HOSPITAL OFFICERS' ASSOCIATION

The second in a series of Tuesday evening lectures sponsored by the Boston City Hospital House Officers' Association will be held in the New Cheever Amphitheater of the Dowling Building, Boston City Hospital, on Tuesday, October 11, at 7 p.m. Dr. Charles P. Bailey, associate professor of surgery, Hahnemann Medical College, Philadelphia, will speak on the subject "Commisurotomy for Mitral Stenosis." Drs. Laurence B. Ellis, Dwight E. Harken, and John W. Strieder will lead the discussion.

All interested persons are invited to attend.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A regular meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, on Tuesday, October 11, at 8 p.m.

Dr. Seymour S. Kety, professor of clinical physiology, University of Pennsylvania School of Medicine, will speak on the subject "Physical and Physiologic Factors Regulating the Uptake of Anesthetic Gases."

NEW ENGLAND VENEREAL DISEASE CONTROL CONFERENCE

The New England Venereal Disease Control Conference will be held in the Gardner Auditorium, State House, Boston, on Wednesday, October 12.

PROGRAM

Morning Session (10 00 a.m. to 12 00 noon)

The Effectiveness of the Multiphase Screen-Testing Program as a Syphilis Case Finding Mechanism

Funds for Syphilis-Control Activities in the Light of a Consistently Declining Reported Morbidity

Evaluation of American Venereal-Disease-Control Activities

Interstate Premarital Regulations and Standard Certificate — A Progress Report

Promiscuity — A Psychiatric Approach

Afternoon Session (2 00-4 00 p.m.)

Newer Experimental Treatment Schedules of Syphilis

The Immobilization Test of *Treponema pallidum* and Practical Application

The Management of Neurosyphilis

Nonspecific Urethritis

The Present-Day Treatment of Syphilis

MASSACHUSETTS CHAPTER, AMERICAN ACADEMY OF GENERAL PRACTICE

The annual meeting and fall clinical program of the Massachusetts Chapter of American Academy of General Practice will be held in Boston on October 19. The morning program will be held at the Massachusetts General Hospital, with medical and surgical clinics by the staff of the hospital. The luncheon, afternoon lecture program and banquet will be held at Hotel Puritan. Mr. Mac F. Cahal, executive secretary of the American Academy of General Practice, Kansas City, will be the speaker.

CONFERENCE OF PROFESSORS OF PREVENTIVE MEDICINE

The annual meeting of the Conference of Professors of Preventive Medicine will be held in New York City on October 24. Luncheon and afternoon sessions will be held in Parlor 1, Hotel Statler. Dr. David D. Rutstein, of Boston, is secretary.

PEDIATRIC SEMINAR FOR PHYSICIANS AND GENERAL PRACTITIONERS

A pediatric seminar for pediatricians and general practitioners will be held on November 23 and thereafter every second and fourth Wednesday of the month at 7 p.m. in Amphitheater 3A of the White Building, Massachusetts General Hospital, by the staff of the Children's Medical Service, Burnham Memorial Hospital for Children, Massachusetts General Hospital.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3-MAY 19 Massachusetts Department of Mental Health, Postgraduate Seminar in Neurology and Psychiatry. Page 286 issue of August 18.

OCTOBER 7 Veterans Administration Course in Clinical Electrophysiology. Page 510, issue of September 29.

OCTOBER 10 Lay Meeting on Diabetes Detection. Notice above.

OCTOBER 10-21 New York Academy of Medicine. Page 510 issue of September 29.

OCTOBER 11 Boston City Hospital House Officers' Association. Notice above.

OCTOBER 11 New England Society of Anesthesiologists. Notice above.

OCTOBER 11-15 American Society of Clinical Pathologists. Drake Hotel Chicago.

OCTOBER 12 New England Venereal Disease Control Conference. Notice above.

OCTOBER 13 Mononucleosis. Dr. Andrew Contratto. Pentucket Association of Physicians. 8 30 p.m. Haverhill.

OCTOBER 14 Tuberculosis Rehabilitation Society. Page 434 issue of September 15.

OCTOBER 19 Massachusetts Chapter American Academy of General Practice. Notice above.

OCTOBER 24 Conference of Professors of Preventive Medicine. Notice above.

OCTOBER 24-26 National Gastroenterological Association. Page 251 issue of August 11.

OCTOBER 24-28 American Public Health Association. Page 251 issue of August 11.

OCTOBER 28 Massachusetts Psychiatric Society. Page 434 issue of September 15.

NOVEMBER 2 New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 2-5 Pan-American Congress of Pediatrics. Page 251 issue of August 11.

NOVEMBER 3-5 American Association of Blood Banks. Page xi issue of June 16.

NOVEMBER 7-9 National Society for Crippled Children and Adults. Page 184 issue of July 28.

(Notices concluded on page vi)

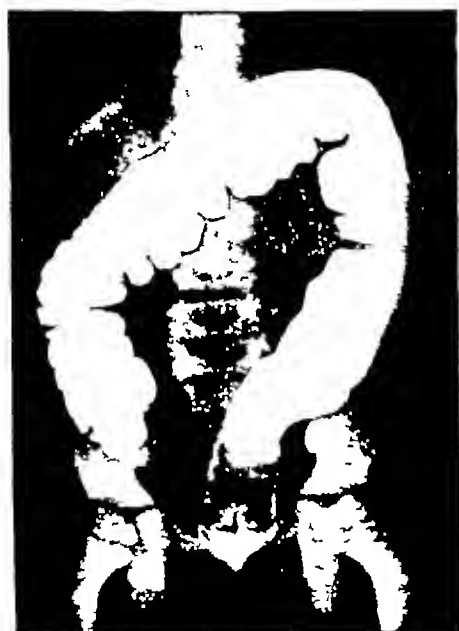


*To a patient with troubles internal
That seemed to be centered subternal,
Said our friend, Dr. Wise, "I must digitalize,
After checking the ads in the Journal"*

those which ordinarily follow chronic, low, partial colonic obstruction. Severe constipation and obstipation are the presenting complaints. Distention, audible and visible peristalsis, cramps and vomiting occur in varying degrees. Large fecal impactions are frequently present in the left side of the colon, whereas the rectal ampulla remains empty. Hirschsprung¹ commented specifically on this finding in his paper. Patients are relieved by colostomy above the area of malfunction, within three or four months dilatation of the colon largely disappears, and hypertrophy diminishes. However, if the colostomy

sigmoid. These important changes in the rectum and rectosigmoid are missed if the lower colon is flooded with too much barium (Fig 1).

Resection of the rectum and rectosigmoid in 34 patients has resulted in 1 postoperative death and in what appears to be complete cure in the remaining 33 patients. This is accomplished by a special operative technic that preserves the anal sphincter.²⁷⁻²⁸ These patients have been followed for periods up to two years. Re-examination by barium enema has demonstrated return of the colon to approximately normal size and contour by the third



A



B

FIGURE 2 Roentgenograms Taken Three Months Postoperatively, Using Routine Barium-Enema Technic. A shows that the dilatation has disappeared. B is a post-evacuation film demonstrating normal emptying.

is closed the syndrome recurs, but reopening of the colostomy again provides relief.

Neuhauser²⁸ was the first to demonstrate by roentgenograms and to attach significance to a narrow segment of rectosigmoid distal to the dilated sigmoid in Hirschsprung's disease. He described this for the first time four years ago and has subsequently demonstrated it in 40 patients with congenital megacolon. This lesion, which Neuhauser and we consider pathognomonic of Hirschsprung's disease, is at times difficult to demonstrate. He recommends that only a small amount of barium should be injected while the patient is being examined under the fluoroscope in an oblique position. One can then observe the narrow, irregular rectum and rectosigmoid distal to the markedly dilated

postoperative month (Fig 2). More important, post-evacuation films show essentially normal emptying of the colon. Postoperatively, these patients are on normal diets and do not require laxatives, enemas or drugs.

The study of colonic function in these patients would add materially to knowledge of this disease. We have conducted a series of colonic-motility studies, using a multiple balloon technic.²⁹⁻³¹

STUDY OF COLONIC PERISTALSIS IN HIRSCHSPRUNG'S DISEASE

The apparatus used in recording motility was patterned after the apparatus used by Chapman.³¹ It consisted of three ink-writing manometers, each attached by a long catheter to a balloon. Each

parasympathetic depressant drug. Mild cases of Hirschsprung's disease can be controlled medically for long periods, but in severe forms these measures fail.

The second method consists of resection of parts or all of the dilated and hypertrophied bowel.^{16, 18} This procedure is based on the theory that the seat of the disease is the enlarged portion of the colon. Resection is frequently followed by recurrence proximal to the line of resection.^{17, 19} This experience

sults in some patients, there are cases of complete failure to alter the course of the disease.

Finally, several clinics have treated the disease by interruption of the sympathetic pathways to part or all of the colon.^{11, 13, 21-26} This approach was originated by Wade and Royle.¹¹ In 1930 Scott and Morton¹³ described the effects of spinal anesthesia on patients with megacolon. In some clinics evacuation following spinal anesthesia has been considered an indication for lumbar sympathectomy. It is



A

B

FIGURE 1. Roentgenograms of a Patient with Hirschsprung's Disease

A shows the bowel filled with barium in a routine manner. (Note the enlargement of the sigmoid colon and rectosigmoid, which might lead to the erroneous conclusion that the colonic dilatation extends down to the anus.)
B demonstrates the use of a special technique (in the same patient) in which small amounts of barium are instilled slowly into the rectum. (Note the lower segment of bowel, which is narrow and irregular and does not relax during the period of observation, the bowel lumen abruptly expands above this area into the dilated segment.)

coincides with what has been observed in this clinic.²⁰ A total colectomy with ileosigmoidostomy is advocated by some surgeons,¹⁷ even though only a portion of the colon seems to be involved. However, after removal of the entire colon, the ileum has been observed to undergo dilatation and hypertrophy, with recurrence of symptoms. Two patients under our observation, a few months after colectomy and ileosigmoidostomy, showed all the symptoms and signs of Hirschsprung's disease owing to tremendous dilatation of the ileum. In one of these patients an ileostomy was subsequently performed, with complete relief of symptoms and reversal of the changes in the ileum. The second patient, in whom an ileostomy was not performed, succumbed to his disease and at autopsy was found to have marked hypertrophy and dilatation of the terminal ileum. Although colectomy gives satisfactory clinical re-

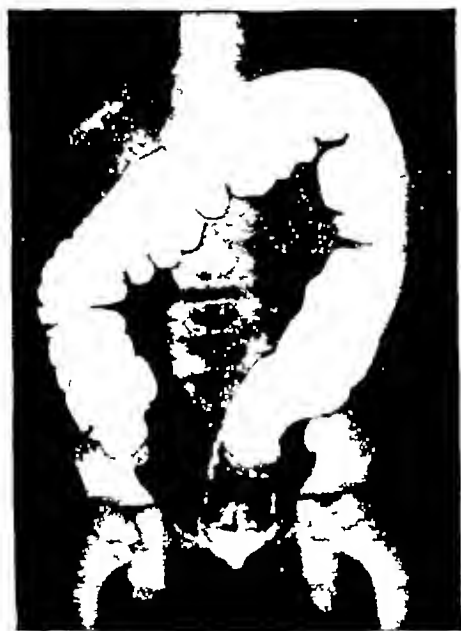
sults, however, that sympathectomy does not reproduce the physiologic effect of spinal anesthesia. Some clinics are treating congenital megacolon by unilateral or bilateral lumbar sympathectomy. Presacral, para-aortic and inferior mesenteric chain resections may be combined with bilateral lumbar sympathectomy and splanchnicectomy.²⁵ The follow-up results of these procedures have not been uniformly satisfactory.

Recently, Swenson et al.^{27, 28} have presented evidence supporting their contention that congenital megacolon is due to malfunction of the rectosigmoid that results in partial colonic obstruction. This obstruction accounts for the dilatation and hypertrophy of the colon, which retains peristaltic function. There is much evidence to support this concept of the etiology of congenital megacolon. The signs and symptoms of Hirschsprung's disease are

those which ordinarily follow chronic, low, partial colonic obstruction. Severe constipation and obstipation are the presenting complaints. Distention, audible and visible peristalsis, cramps and vomiting occur in varying degrees. Large fecal impactions are frequently present in the left side of the colon, whereas the rectal ampulla remains empty. Hirschsprung¹ commented specifically on this finding in his paper. Patients are relieved by colostomy above the area of malfunction, within three or four months dilatation of the colon largely disappears, and hypertrophy diminishes. However, if the colostomy

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A



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balloon was filled with 10 cc of air, and pressure changes were recorded on a kymograph

In 5 patients with Hirschsprung's disease (Group I) colostomy had been performed as a preliminary step in resection of the rectum and rectosigmoid. In this group a Levine tube was introduced through the colostomy and was passed with fluoroscopic aid into the rectosigmoid. A sigmoidoscope was used to bring the tube out through the anus. Balloons attached to separate catheters were then tied to the Levine tube at intervals. By gentle traction the whole apparatus could be positioned so that one balloon was in the splenic flexure, a second in the

after the ingestion of food, and were of equal amplitude in each area, as recorded by the three manometers. Between large waves there were smaller waves, which were recorded from all areas of the bowel tested. The smaller contractions were assumed to be those of segmentation.³²

The recordings from the patients with congenital megacolon exhibited a different pattern (Fig 3B). The two proximal balloons in the splenic flexure and lower descending colon showed peristalsis, as did the controls. This supports our contention that the dilated and hypertrophied colon retains peristaltic function. The recordings from the balloon in the

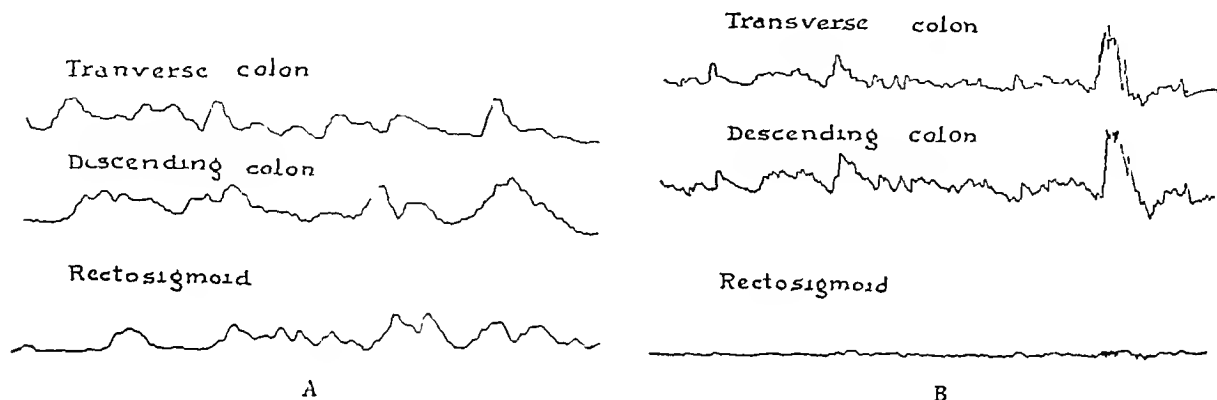


FIGURE 3

A = Tracings from a control patient with colostomy. The upper line records activity of the balloon in the splenic flexure. The middle line records from the balloon in the descending colon, and the lower tracing is from the balloon in the rectosigmoid. Tracings progress from left to right. Note the appearance of large waves progressing from the upper to the lower balloons. Smaller contractions are also present.

B = Tracings from a patient with Hirschsprung's disease in whom a preliminary colostomy had been performed. The recordings are from balloons in the same relative positions as the control patient in Fig 3A. Note that the large waves, which are tracings from the upper two balloons in the dilated and hypertrophied bowel, do not progress into the narrowed rectosigmoid. Small, unassociated waves are recorded from the lower balloon in the narrow lower segment.

descending colon and a third in the narrow portion of the rectosigmoid. The balloons were then inflated and tracings were made. Two patients who had had an intussusception requiring resection and ileo-transverse colostomy of the Mikulicz type were used as controls.

Three patients with Hirschsprung's disease (Group II), in whom colostomy had not been performed, were studied by the insertion of two balloons through the anus. One of the balloons was positioned in the sigmoid and the other in the narrow rectosigmoid. Postoperative as well as preoperative studies were performed in this second group of patients. Control tracings were obtained in a similar manner from 2 patients with normal colons. In all these studies food was given to stimulate colonic peristalsis.

RESULTS OF STUDIES ON COLONIC PERISTALSIS

Group I

Recordings from the control patients with colostomies showed progression of the propulsive peristaltic wave from the transverse colon to the anus (Fig 3A). These waves appeared in groups, usually

narrow rectosigmoid were entirely different, no peristaltic wave was recorded from this site. As compared to the controls, there was a larger rise in the height of the recording baseline when 10 cc of air was injected into the balloon. The higher baseline, indicating increased tonus, changed little if at all during the period of observation, and was interpreted as failure of relaxation of this segment of bowel. In 2 of the patients with Hirschsprung's disease there were no changes whatever in intraluminal pressure from the rectosigmoid segment. In the other 3 patients with the disease there was a rhythmic series of segmental contractions of low amplitude in this area, which was totally dissociated from the peristaltic waves in the descending colon.

Group II

Recordings from the normal control patients with balloons in the sigmoid and rectosigmoid demonstrated forceful peristaltic waves, which progressed to the anal sphincter. In 3 patients with Hirschsprung's disease who had had no preliminary colos-

tomy, peristaltic waves were recorded from the dilated sigmoid, but these waves did not enter the narrow rectosigmoid. No contractions whatever were recorded from the lower balloon in 1 of these patients. In another, slight rhythmic segmental contractions were recorded from the balloon in the narrow segment. These contractions were independent of the powerful contractions in the dilated sigmoid. In the third subject normal contractions, not related to sigmoid peristalsis, were recorded from the rectosigmoid. Postoperatively, this group yielded tracings identical with those of the normal controls. Powerful peristaltic waves were recorded, which now progressed to the anus.

Attempts have been made a number of times to relate the pathogenesis of congenital megacolon to abnormality of the myenteric plexus. Dalla Valle,³³ in 1920, described a case of congenital megacolon in which almost no myenteric plexuses were seen in the sigmoid and ascending colon. Ganglion cells were present in the hepatic flexure and transverse colon. Robertson and Kernohan³⁴ described absence and deformity of myenteric ganglion cells in a case of congenital megacolon. Tiffin, Chandler and Faber³⁵ reported localized absence of myenteric plexus in the undilated sigmoid; ganglion cells were normally distributed in the proximal, dilated colon. Recently, Zuelzer and Wilson³⁶ made similar observations in cases of congenital intestinal obstruction in infancy. Both the latter studies suggest that some cases of congenital megacolon are due to agenesis of myenteric plexus in the lower bowel.

A survey of the distribution of myenteric ganglion cells was made in 7 of the cases reported. The excised colonic segments were examined by the removal of five longitudinal strips from the entire length of each segment. The strips were divided into consecutive numbered blocks approximately 2.5 cm. in length and sectioned parallel to their long axis. At selected intervals consecutive numbered blocks were taken along the short axis of the bowel. Formalin-fixed and Klotz-fixed tissues were used, and sections stained with hematoxylin and eosin. When indicated, blocks were serially sectioned at intervals of 10 microns to confirm the absence of ganglion cells.

When ganglion cells are present the sections from blocks taken from different areas of a given circumference show that the myenteric plexus forms a fairly continuous sheet between the two layers of muscle. Zuelzer and Wilson³⁶ point out that ganglion cells were found in all sections at every level in 10 normal colons. Every section of colon taken from random areas in 50 consecutive autopsies in our files showed ganglion cells.

Five of the bowels presented a similar pattern in ganglion-cell distribution. The myenteric plexus was present in the dilated proximal portion and absent in the distal narrow portion. The absence of ganglion cells was not closely related to the level of

narrowing of the lumen. Frequently, the cells disappeared proximal to this. One case showed no ganglion cells in any portion of the specimen. In another, exhibiting strong independent rectosigmoid contractions, the pattern was different. Ganglion cells were present throughout the distal narrow segment. Proximal to this in the dilated segment a zone measuring 4 or 5 cm. in length was found devoid of ganglia. Above this, ganglion cells were again present.

The distribution of the ganglion cells, when correlated with the motility studies, suggests that absence of the peristaltic-wave progression may be due to absence or abnormal distribution of the myenteric plexus in a segment of the colon. It is not suggested that this occurs in all cases of congenital megacolon.

CONCLUSIONS

In performing motility studies we have observed that complete quiescence of the normal colon may persist for as long as six hours. A simple method for initiating normal contractions is the ingestion of food. Tracings from a single balloon are of no significance, since no record of peristaltic progression is obtained. In a patient with Hirschsprung's disease, only a multiple-balloon technic will demonstrate that propulsive waves are present in one part of the colon and absent in another.

In the past, the emphasis on Hirschsprung's disease has been directed to the dilated and hypertrophied colon. It is our contention that the primary lesion rests in the distal, nondilated segment, despite the fact that grossly this area appears normal. We have demonstrated in control patients that groups of strong peristaltic waves progress from the transverse colon to the anus. In 8 patients with Hirschsprung's disease we have recorded strong peristaltic waves in the dilated and hypertrophied colon. In 5 patients progression of the peristaltic waves along the enlarged segment was evident. In none of the 8 patients with Hirschsprung's disease did the peristalsis enter the narrow distal segment, which did exhibit increased tonus.

We believe that the absence of normal propulsive waves in the rectum and rectosigmoid constitutes a physiologic defect that results in chronic obstruction. This malfunctioning segment is identical with the narrow, irregular bowel visualized by roentgenograms. There appears to be a correlation between the absence of ganglion cells in areas of the rectosigmoid and the physiologic defect.

Removal of the narrow, irregular rectum and rectosigmoid by a special surgical technic in 34 patients has resulted in 1 postoperative death and what appears to be complete cures in 33 patients. As early as three months postoperatively the colon is essentially normal by barium-enema examination. In 3 patients we have demonstrated normal colonic peristalsis postoperatively by balloon studies.

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TREATMENT OF TYPHOID FEVER WITH CHLOROMYCETIN*

Results in Four Cases and in a Chronic Carrier

HARVEY S COLLINS, MD,† AND MAXWELL FINLAND, MD‡

BOSTON

CHLOROMYCETIN (Chloramphenicol) is a new antibiotic that, like aureomycin, has been of particular interest because it is effective when given by mouth and because its range of antimicrobial action includes not only many common pathogenic bacteria but also the rickettsias and the viruses of the psittacosis-lymphogranuloma-venereum group^{1,2} Of added interest is the fact that chloromycetin has been synthesized³ and that the fermentation and synthetic products have been shown to have the same activity⁴

In a preliminary report, Woodward and his co-workers⁵ found that chloromycetin exerted a specific therapeutic effect in 10 patients with typhoid fever whom they treated in Malaya In another group of cases of this disease, most of them treated in Mexico,

McDermott, Knight and Ruiz-Sanchez⁶ observed that the administration of chloromycetin was uniformly followed by prompt recovery, which, in most cases, was dramatic These observations were somewhat in contrast to experiences reported with aureomycin administration in typhoid fever, the results of which have been irregular and, on the whole, rather unimpressive⁶⁻⁹ When a supply of chloromycetin was made available,⁸ a study of its effects in typhoid fever was undertaken, and the findings in the first 4 patients and in a typhoid carrier are reported below

MATERIALS AND METHODS

The first 3 patients were treated at the Massachusetts General Hospital, and we are deeply indebted to Dr J H Means and to many other members of his visiting and resident staffs for their interest and co-operation and for the privilege of studying and reporting these cases The fourth patient was

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†Aided by a grant from the United States Public Health Service

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§Provided through the courtesy of Dr E. A. Sharp of Parke Davis and Company Detroit, Michigan

treated on one of the medical wards of the Boston City Hospital, and the typhoid carrier was studied at the South Department of that hospital through the courtesy of Dr Edwin H. Place.

Specimens of blood, stools and urine were obtained before treatment and at intervals after treatment as indicated and feasible. The isolation and identification of the organisms from the first 3 patients were carried out in the laboratory of Dr L. Dienes, and those in the other 2 patients were done by Marion E. Lamb and A. Kathleen Daly. The sensitivity of the strains was tested by a serial dilution method on the surface of agar plates, a prepara-

improvement corresponded to the fall in temperature and convalescence was uneventful. The blood culture taken on the day chloromycetin was started was positive, but all other blood and stool cultures were negative for *Salmonella typhosa*. There were no untoward effects from the chloromycetin.

CASE 2 M. M., a 38-year-old Italian woman, was admitted to the hospital on April 27, 1949. For the previous 10 days she had been having frontal headache and fever with profuse sweating, and for 5 days she had general malaise, chilli sensations, nausea, vomiting and constipation. During the last 3 days she also complained of constant boring pain in both flanks, with radiation toward the right lower quadrant, and, in addition, she developed a dry cough with substernal soreness. On the day before entry she had a shaking chill. Her physician gave her 2 injections of 300,000 units of crystalline procaine penicillin and also oral doses of sulfadiazine, 1 gm

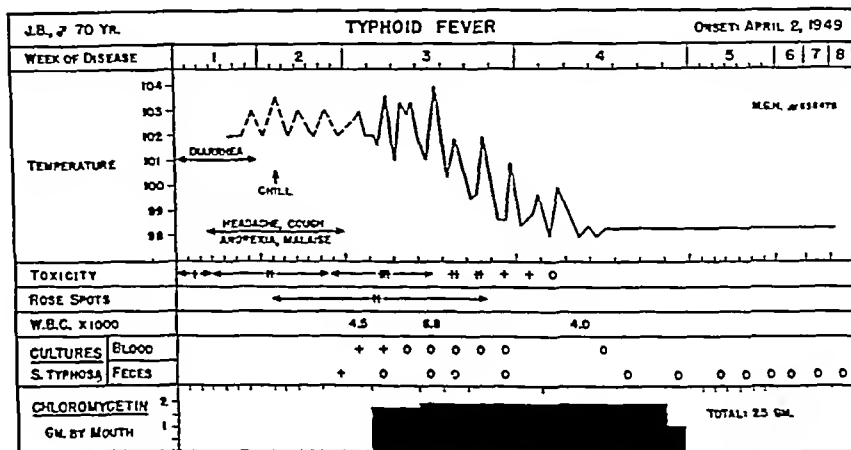


FIGURE 1 Course, Treatment and Laboratory Findings in Case 1

tion of crystalline chloromycetin provided by Dr E. A. Sharp being used.

CASE REPORTS

CASE 1 J. B., a 70-year-old Lithuanian, entered the hospital on April 16, 1949. For the preceding 2 weeks he had felt poorly and had been having 4 to 6 loose, nonbloody bowel movements each day. He continued to work during the first 4 days, but then, because of weakness, a slight cough, headache, anorexia and fever, he had to stay at home. His daughter, a nurse, found his temperature to range between 102 and 103°F daily during the next 10 days. She also noticed that he was apathetic and slept much more than usual. His headache and diarrhea persisted. On April 10 he had a severe shaking chill, and at that time some "red spots" were noted on his back. The family physician obtained blood and stool specimens for cultures, and when these were reported positive for typhoid bacilli he sent the patient to the hospital.

On admission the patient appeared apathetic, and the only significant findings on physical examination were a few rose spots on the abdomen and an enlarged liver. The temperature was 102.5°F, the pulse 90, and the respirations 25. The course, therapy and relevant laboratory findings are shown in Figure 1. Chloromycetin was begun on April 17, with doses of 0.5 gm by mouth every 4 hours for 6 doses and thereafter every 6 hours. A total of 25 gm was given over a period of about 12 days. The patient began to look and feel better after 3 days, and then the temperature fell gradually over the next 5 days and remained essentially normal thereafter. The pulse rate dropped from 90 to 70 during this time. The rose spots also faded over the course of the first week. General

every 4 hours, but when, after 2 days of this therapy, she failed to improve, he sent her to the hospital.

At the time of admission she was acutely ill. The positive findings on physical examination included a few small red lesions (petechiae) in the left palpebral conjunctiva and on the soft palate, marked abdominal distention without any localized tenderness and a palpable spleen.

The temperature was 105.2°F, the pulse 120, and the respirations 30. The blood pressure was 125/70.

The treatment, course and significant laboratory findings are shown in Figure 2. Sulfadiazine was discontinued after the patient entered the hospital, and penicillin 2 days later. On April 30, when the blood cultures taken on the previous days were reported as showing typhoid bacilli, oral administration of chloromycetin was started. She was given doses of 0.5 gm every 2 hours for 8 doses, and then for every 3 hours for 8 days and every 6 hours for 4 more days. When this therapy was stopped on May 13, she had received a total of 44 gm.

The course during the first few days was rather stormy. On May 2, she had a shaking chill and, because of the severe distention and vomiting, was suspected of having an intestinal perforation, the white-cell counts, however, remained low, and no air could be demonstrated under the diaphragm on x-ray study. Shortly thereafter, the patient's cough became worse and productive of thick mucopurulent sputum, cultures of which yielded a predominant growth of *Escherichia coli*. Roentgenograms of the lungs showed partial atelectasis of the right lower lobe, with marked elevation of the diaphragm on that side. Although the pulmonary signs persisted for 2 weeks, the patient's general condition began to improve rapidly after the first week of therapy. The temperature and pulse rate gradually reached normal during this time and remained so thereafter. Blood cultures taken during the

blood pressure was 125/75. No rose spots were seen, but the edge of the spleen was felt about 4 cm below the costal margin. The highlights of the course, therapy and laboratory findings, are shown in Figure 3.

On May 3 after the earlier blood and stool cultures had been reported as positive for *S. typhosa*, oral chloromycetin therapy was started. Doses of 1.0 gm each were given every 6 hours for 8 days and 0.5 gm every 6 hours for 5 more days. A total of 45 gm had been given when this therapy was stopped on May 16. On the 3rd day of this treatment the patient appeared more alert, she felt much better generally, and the stools became less frequent and less watery. The temperature dropped sharply on that day and then gradually until it became and stayed normal 3 days later. There was some fresh blood and an occasional clot in some of the stools passed during the first day, presumably from bleeding hemorrhoids. Culture of the stool obtained on the day after chloromycetin was started was positive, but all other blood, stool and urine cultures made during this course of therapy were negative for *S. typhosa*.

Convalescence appeared to be progressing uneventfully, and plans were completed for transfer of the patient to a

brisk hemorrhages from old hemorrhoids and a fistula in ano. These were repaired surgically before the patient left the hospital. Cultures of blood taken during the first 3 days and of stools taken during the first 2 days of this course of chloromycetin were positive, but all subsequent cultures, including that of some bile obtained by duodenal tube 2 days after the course was ended, were negative for *S. typhosa*.

CASE 4 H S, a 51-year-old Russian resident of Peabody, Massachusetts, was sent to the hospital on May 21, 1949. Her illness had begun on April 30 with weakness, chilliness and fever. During the 1st week she had chills, profuse sweats and mild delirium each night. She also experienced pain in the left calf and swelling of the lower leg, which made her stay off of her feet much of the time. During the 2nd week she allegedly improved, and the swelling and pain in the leg subsided but she continued to have the nocturnal chills and sweats, with occasional delirium. Her bowel movements became watery but did not increase in frequency. There were periods during each day when she became pale and faint, and she felt unsteady most of the day although she continued to do some of her housework. On May 6 a physician found the

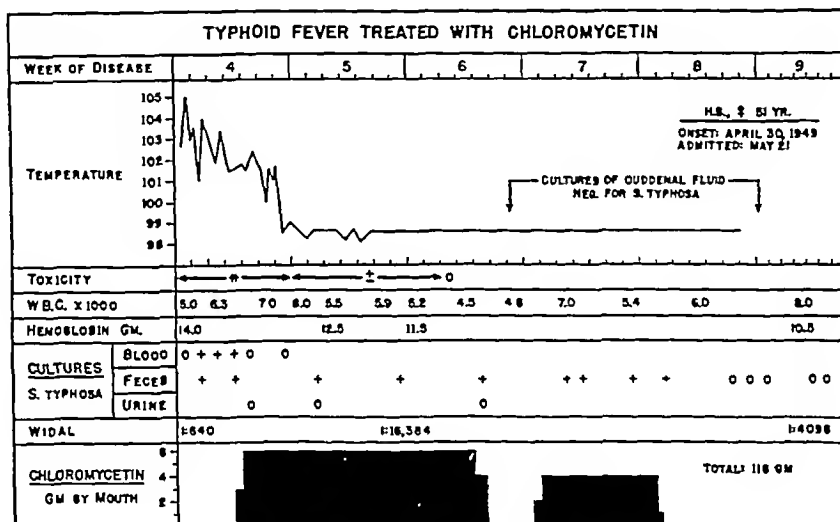


FIGURE 4. Hospital Course in Case 4.

This patient received another course of chloromycetin for a week for thrombophlebitis shortly after discharge from the hospital. Culture of a stool obtained at the end of this course was positive for *S. typhosa*.

nursing home to recuperate when, on May 23, she again had a low-grade fever and headache. On the following day the temperature rose to 104°F, and a search for possible causes of this fever disclosed pyuria and bacilluria, a culture of the urine yielding *Esch. coli*. She was then placed on small doses of a sulfonamide. However, it was not until May 25, when cultures of blood and stools taken on the previous days were reported as positive for *S. typhosa*, that it was realized that she was suffering a relapse of the typhoid fever. The temperature by then had risen to 106°F, and the pulse to 120. The spleen which had already receded, was again palpable, headache and severe diarrhea recurred, and the patient again became drowsy and apathetic.

A second course of chloromycetin was then started, this time with 1 gm every 4 hours for about 2 weeks and every 6 hours for an additional week. This course of treatment ended on June 12, after 96.5 gm had been given. There was a sharp drop in temperature 48 hours after the treatment was resumed. During the following 4 days the temperature rose only to 100 or 101°F each day, the patient showed distinct and progressive improvement. There was marked nausea and vomiting during the first 2 days and persistent nausea throughout most of this course of treatment. During the next 2 weeks the patient was noted to have definite glossitis and cheilitis suggesting vitamin B deficiency. She also had some

temperature to be 103°F and prescribed penicillin by mouth, which she took without relief. The symptoms continued unchanged until she was sent to the hospital.

On admission, the patient appeared alert, co-operative and rather hyperactive. Her skin was clear, warm and dry. There were a few fine crepitant rales at the lung bases posteriorly. The abdomen was distended with gas, peristalsis was active, the liver edge was felt about 2 fingerbreadths below the right costal margin, and the spleen was not felt although to percussion it reached the left costal margin. There were large varicose veins of both legs but no evidence of inflammation, and there was no edema. The temperature was 105°F, the pulse 84, and the respirations 20. The blood pressure was 100/60. The patient was a diagnostic problem until the results of the blood and stool cultures taken on the day after admission were reported as positive for *S. typhosa*. The course, therapy and relevant laboratory findings are shown in Figure 4.

Chloromycetin was started on May 24, and doses of 1 gm every 4 hours were given until June 8. Therapy was stopped for 3 days in order to obtain cultures of bile and then resumed in doses of 1 gm every 6 hours until it was discontinued on June 19, after a total of 116 gm had been given. The temperature dropped to normal on the third day after the chloro-

mycetin was first begun and remained so. The patient continued to look, feel and eat fairly well until after the chloromycetin was started, when she began to complain of dizziness, a "heavy feeling in the head," sour taste in the mouth, "heartburn" and a complete lack of desire for food. She also became constipated. Most of these symptoms continued until the antibiotic was discontinued for the first time, and she vomited only on 1 day during this period. During the time when she was not taking chloromycetin, her dizziness and heartburn stopped and her appetite improved, but these symptoms and sour taste returned after she had been on the lower dosage for a week.

The blood and stool cultures taken on the day treatment was started were again positive for *S. typhosa*, but 2 subsequent blood cultures taken during the febrile period were negative. Cultures of the stools, however, continued to show *S. typhosa* throughout the entire period of chloromycetin therapy. Several stools obtained during the next 2 weeks were negative for typhoid bacilli, as were 2 specimens of duodenal content. The latter results, however, were vitiated by the fact that there was an admixture of acid gastric content.

Convalescence appeared to be uneventful when the patient was discharged home on July 1. Four days later thrombophlebitis of the left external saphenous vein, with fever and marked edema of the leg, occurred. She was admitted to another hospital, where another course of chloromycetin was given—about 2 gm. a day for 7 days. The temperature dropped rapidly from 103°F to normal, and the tenderness and swelling subsided slowly. A stool specimen sent to the State Bacteriological Laboratory after the end of this course of chloromycetin was reported as positive for typhoid bacilli and several additional cultures of stools obtained during the next 2 months were also positive for *S. typhosa*.

CASE 5 M. E. was the 73-year-old chronic typhoid carrier previously reported.⁷ Two courses of aureomycin, one during April and May 1948, and the other in July and August of that year, the latter course given after a cholecystectomy, failed to clear the patient's stools of typhoid bacilli. She was given a course of 33.5 gm. of chloromycetin by mouth, 0.5 gm. every 6 hours from March 20 to April 8, 1949. She had slight diarrhea throughout this period, but no other untoward effects. During the 6 months immediately preceding the course of chloromycetin, 25 of the 31 stools that were cultured were positive for *S. typhosa*. Between March 22 and April 18 a total of 10 stools were cultured, and all were negative for typhoid bacilli. However, 3 of 4 stools that were cultured during the following week again were positive.

The effects of chloromycetin in each of these 5 cases may be summarized briefly.

In Case 1 treatment was undertaken early in the third week of the disease with doses of 2 gm. a day. Defervescence occurred by lysis between the third and ninth days of therapy, with steady symptomatic improvement over this period. Typhoid bacilli could no longer be obtained by culture from the blood or feces after the first day of therapy, and convalescence was uneventful. There were no untoward effects from the chloromycetin in this case.

In Case 2 treatment with daily doses of 4 gm. of chloromycetin was started at the end of the second week of illness. The patient continued to be acutely ill for about a week, and the temperature dropped progressively between the fifth and eighth days of treatment. Typhoid bacilemia was demonstrated during the first two days of this therapy, but cultures of blood, urine and stools obtained after that time were all negative for *S. typhosa*, with the possible exception of the blood culture made on the second day after the treatment was stopped. Rather severe and persistent vomiting occurred during the first week of chloromycetin administration, and

may have been responsible for the delayed response in this patient.

In Case 3 there was a full-blown clinical and bacteriologic relapse after an apparently good response to an initial course of chloromycetin that was begun in the middle of the second week of the disease and consisted of 43 gm. given over a period of thirteen days. Improvement again followed quite promptly after a second and more intensive course of chloromycetin was started. There were no untoward effects from the first course, but the patient was nauseated throughout most of the second course and vomited several times soon after the larger dosage was started. This patient also experienced glossitis and cheilitis that may have been attributable, in part, to the antibiotic.

In Case 4 treatment with 6 gm. of chloromycetin daily was started during the middle of the fourth week of the disease, and the patient maintained for two full weeks on that dosage and for an additional week on 4 gm. a day. She became and remained afebrile after the third day of this therapy, but she continued to shed typhoid bacilli in her stools throughout the period of treatment and the organisms were recovered again more than three months later. The effect of therapy on the symptomatology was difficult to evaluate in this case. Distressing gastric symptoms accompanied the larger doses of the antibiotic, but were less marked and somewhat delayed during the second course when smaller doses were given.

In the chronic carrier, typhoid bacilli could not be isolated from the stools during the two weeks of chloromycetin therapy and for a brief period thereafter. The organisms then reappeared in the stools and could be recovered quite regularly. This patient experienced mild diarrhea but no upper gastrointestinal symptoms while taking the antibiotic.

SENSITIVITY OF THE STRAINS

The strains of *S. typhosa* that were isolated from these patients and tested were found to be about equally sensitive to chloromycetin. They were all partially inhibited in concentrations of 4 microgm. per cubic centimeter, some of them were completely inhibited in the same concentration, whereas others required twice that concentration for complete inhibition. All strains isolated from different sources and at different times from the same patient showed the same sensitivity to chloromycetin. There was no tendency for the development of increased resistance during treatment.

DISCUSSION

It is quite apparent from the results obtained in this small group of patients that chloromycetin, although it may have had a beneficial effect on the course of the acute disease, did not produce the dramatic effects that were expected. The persistence of the organisms in the stools in Case 4 and in the

carrier, the clinical and bacteriologic relapse in Case 3 and the rather slow defervescence in 3 of the 4 acute cases indicate that chloromycetin, like aureomycin, still leaves much to be desired as a curative therapy for typhoid fever. Relapses with bacteremia were also noted in 2 of the 10 chloromycetin-treated patients reported from Malaya⁵ and were not uncommon after treatment with either chloromycetin or aureomycin among the cases studied by McDermott, Knight and Ruiz-Sanchez.⁶ Serious complications, an intestinal hemorrhage in 1 case and perforation in another, occurred on the fourth and the second afebrile day, respectively, in 2 additional chloromycetin-treated patients from Malaya.⁵

The possibility that strain differences account for the variations in response to treatment was considered. Phage typings* indicated that the strains from the acute cases all belonged to the same phage type (E), whereas the carrier's strain was of a different type (A). Differences in response dependent on the host or on the nature of the lesion at the time treatment was started cannot be ruled out. With respect to the latter, McDermott et al.⁶ considered that aureomycin exerted an effect on the course of the infection particularly when treatment was started during the first ten days of the disease. These effects were seldom dramatic, however, and in well established infections (third week) were frequently negligible. Chloromycetin administration, by contrast, was uniformly followed by prompt and usually dramatic recovery in their experience.⁶

Although McDermott and his colleagues found chloromycetin to be markedly superior to aureomycin as a therapeutic agent in typhoid fever, our own limited experience to date shows that, except for a lower incidence of gastric symptoms with chloromycetin, the difference between the effects of these antibiotics has not been so striking. Such differences may become more apparent, however, with further experience in a larger group of cases. Diagnosis and initiation of treatment early in the disease and possibly the use of maximal doses from the start and continued for long periods may be determining factors in the success of both these agents in some cases.

The recent studies of Seligmann and Wassermann¹⁰ on the action of chloromycetin on sal-

monella are of interest in relation to the findings in the present cases and particularly with respect to the failure to eliminate typhoid bacilli from the feces in Case 4 and in the chronic typhoid carrier. All of 23 salmonella types that these authors studied, including *S. typhosa*, were sensitive to 2 or 4 microgm. However, in experimental infections with *Salmonella typhimurium* in mice, chloromycetin failed to control the infection and exerted no influence on the intestinal flora when given orally or subcutaneously even in large doses and when treatment was started immediately after infection.

SUMMARY

The effect of chloromycetin (Chloramphenicol) on the clinical course and laboratory findings in 4 patients with typhoid fever is discussed. Clinical improvement and defervescence began on the third day after treatment had been initiated in each case and was complete after about a week of therapy. One of the patients had a relapse with bacteremia after the temperature had been normal for two weeks. A second patient continued to shed typhoid bacilli in the stools throughout three weeks of chloromycetin administration and again during convalescence.

Chloromycetin, given in doses of 2 gm a day for two weeks, failed to cure a chronic typhoid carrier whose gall bladder had previously been removed.

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*The phage typings were carried out by Dr. P. R. Edwards in the Enteric Bacteriology Laboratory of the Communicable Disease Center of the United States Public Health Service in Chamblee, Georgia. We are indebted to Dr. Rita M. Kelley for sending out the strains from the first 3 patients.

USE OF DIETHYLSTILBESTROL TO PREVENT FETAL LOSS FROM COMPLICATIONS OF LATE PREGNANCY*

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THE present communication deals with further progress in a clinical evaluation of our concept concerning the action of diethylstilbestrol in human pregnancy. Analyses of results in 632 pregnancies during which this drug was given in the manner recommended by us have been reported.¹ In 491 of these cases stilbestrol was administered for the prevention or treatment of abortion. A preliminary report was included, however, upon its use in 95 patients for the purpose of preventing complications of late pregnancy. These 95 cases are included in the present study of a total of 180 women in whom the indication for therapy was diabetes, essential hypertension, nephritis or a past obstetric history of pre-eclampsia, eclampsia, premature delivery or unexplained intrauterine death of the fetus.

The use of stilbestrol in pregnancy is based upon experimental evidence for its progesterone-stimulating effect in rats² and in pregnant women.³⁻⁵ The indications for such therapy and the dosage schedule recommended have been presented.¹ We were particularly interested in its possible value for the prevention of complications of late pregnancy, since a premature deficiency of the placenta in the secretion of estrogen and progesterone before and during late-pregnancy toxemia, premature delivery and intrauterine death had been shown by our own studies and confirmed by others.⁶ We have emphasized the fact that whatever the primary etiologies of these complications may be, a premature deficiency of estrogen and progesterone sooner or later is involved and becomes an intermediate contributing factor. Moreover, we have laid emphasis upon the reciprocal relation between vascular supply to the uterus and hormonal support, adequate vascularity being as essential for the normal production of the placental steroid hormones as adequate hormonal support for the increased vascular demands of the pregnant uterus. By supplying an extra stimulus for the secretion of estrogen and progesterone, we are attempting to combat only one of the contributory factors of the final syndrome. If a more normal secretion of estrogen and progesterone is accomplished, however, the vascular deficiency should be minimized, since the combined

action of these two steroid hormones is characteristically one of vascular and myometrial growth. Experimental and clinical experience indicates that neither one of them alone could accomplish the degree of uterine growth and vascularity required in late pregnancy. Improved clinical results in themselves, therefore, would provide added support for the stimulative effect of stilbestrol upon the placental secretion of both the sex steroids.

From these considerations it is apparent that stilbestrol administration could not be expected completely to prevent late-pregnancy complications. By combating one of the contributory factors in vascular deficiency, however, we might well postpone, if not entirely avert, the onset of the final clinical abnormality. This in itself would result in less damage to the mother and a greater chance for fetal survival.

SOURCE OF CLINICAL MATERIAL

We are indebted to 58 obstetricians for the records of 104 of the 180 pregnancies to be reported, our method of acquiring this information being the same as that previously described.¹ The other 76 women were patients referred to us at the Boston Lying-in Hospital, where they received their prenatal and obstetric care. All of them took stilbestrol by mouth according to the dosage schedule used in our first study.¹ In no case was the therapy begun later than the nineteenth week and in the majority it was given from the start of the seventh to twelfth weeks. *We do not recommend diethylstilbestrol except as a preventive measure for late-pregnancy toxemia.* This statement is based on both theoretical grounds and actual experience.^{1, 4}

CLINICAL RESULTS

Table 1 presents the over-all data on the 180 women to whom stilbestrol was given to prevent late-pregnancy complications. Only 10 were primigravidae; 4 of 14 diabetic patients and 6 of 50 who had hypertension, either essential or secondary to nephritis. The other 170 patients had had a total of 380 previous pregnancies, of which only 28 (7.4 per cent) had progressed normally to term with no complications involving either the mother or child. Fifteen per cent had spontaneously aborted. The other 78 per cent of previous pregnancies had been complicated by spontaneous premature delivery, unexplained stillbirth or toxemia. The total

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§E. R. Squibb and Sons supplied the 25.0-mg. tablets of stilbestrol used in this study.

fetal salvage from these 380 pregnancies had been 116 living babies or 30 per cent

Although the over-all outcome of the present pregnancies on stilbestrol is obviously a great improvement over the past obstetric histories a fair evaluation of the effect of stilbestrol administration cannot be made without a more detailed analysis, as pointed out below

In evaluating the results of stilbestrol therapy for threatened and chronic abortion¹ we had reliable figures on the spontaneous cure rates of these conditions as a basis for statistical analysis of our data. No such generally accepted figures are available, so far as we know, as a basis for evaluating any prophylactic therapy against

essential or secondary to renal disease. These were women either known to have essential hypertension or nephritis or found to have a blood pressure of 140 systolic, 90 diastolic or above in at least two readings prior to the twenty-second week. The ages ranged from twenty to forty-four years, and 33 of them (66 per cent) were over thirty years old. Seven had chronic nephritis. Forty-four of these women (88 per cent) were multigravidas with poor obstetric histories. There were no twins in past deliveries, but 3 of the 50 women had twins while on stilbestrol making a total of 53 possible infants.

By stimulation of maximum secretion of the placental steroid hormones through stilbestrol administration, it was postulated that the uterine vascular deficiency associated with hypertension might be at least partially counteracted and obstetric complications thereby minimized. The results of stilbestrol therapy are presented in Table 2 and may be evaluated by comparison with the past 105 pregnancies of these same patients when no stilbestrol was administered. Inasmuch as hypertension is a progressive disease, this means of evaluation appears to be valid.

Fetal loss was reduced from 53 to 15 per cent. Cosgrove and Chesley² have placed the fetal loss in all pregnant women with essential hypertension, regardless of severity, at 38 per cent. At the Boston Lying-in Hospital between 1932 and 1948 the total fetal loss in 138 hypertensive patients was 64 per cent with a 40 per cent mortality in the 84 babies

complications of late pregnancy. In a planned study that is being separately reported,³ the course and outcome of the pregnancies of 387 primigravidas on our dosage schedule of stilbestrol are compared with those of 555 synchronous control primigravidas who received the same prenatal and obstetric care. In this study statistical analysis was possible and showed a highly significant difference between treated and control cases in the matter of the incidence and severity of toxemia and of fetal loss from late-pregnancy complications. From these results it seems safe to assume that the use of diethylstilbestrol should be effective as a preventive measure in patients in whom complications of late pregnancy may be anticipated. In evaluation of the present study on just such cases however certain difficulties are encountered. Lacking reliable information on spontaneous cure rates and considering the heterogeneous nature of the clinical material we can only break down the data in various ways that seem to warrant a comparison of the outcome on stilbestrol with the past obstetric histories of the same patients.

Essential Hypertension and Nephritis

Of the 180 patients observed, 50 were given stilbestrol because of pre-existing hypertension either

TABLE 2 *Prophylactic Administration of Stilbestrol to 50 Patients with Pre-existing Hypertension*

COMPLICATION	PAST OBSTETRIC HISTORY		PREGNANCY ON STILBESTROL*	
	NO OF CASES	PER-CENTAGE	NO OF CASES	PER-CENTAGE
Abortions†	24	23	4	7.5
Spontaneous premature delivery‡	20	28	15	26
Death from prematurity	6	(14.20)	0	(0)
Stillbirth (unexplained)	55	5.7	0	0
Superimposed toxemia	1	2	14	28
Fetal loss from toxemia	1	(12.22)	1	(7)
None	1	12	24	48
Total fetal loss	56	5	8	15*

*Including 2 pregnancies making the fetal loss 8 out of 53 possible infants. There were no multiple pregnancies in the 10 cases with past obstetric histories.

†At less than 22 weeks.

‡At less than 37 weeks.

that reached viability. * Forty-nine infants of the stilbestrol-treated hypertensive patients attained viability. Only 4 of these, 8.1 per cent, were lost, as against a 40 per cent mortality among their 81 previous babies that had reached viability. It seems clear therefore, that the fetal loss in these 50 stilbestrol-treated patients was considerably less than might have been expected. The factors involved (Table 2) are discussed below.

*We are indebted to Dr. William J. Mulligan for collecting this information from the record room of the Boston Lying-in Hospital.

The incidence of spontaneous delivery prior to the thirty-seventh week was not reduced, probably because many patients who would have aborted without stilbestrol carried their pregnancies beyond the twenty-second week but not to term. Fetal mortality from prematurity, however, was less than half that of the previous pregnancies. As shown below, there is good indication that the premature baby of a stilbestrol-treated mother is unusually mature for its gestational age.

There were 6 unexplained stillbirths in the past obstetric histories of these patients, an incidence of 5.7 per cent. No stillbirths occurred on stilbestrol.

Any rise in blood pressure during the last two months above the level noted prior to twenty-two

third, that of an infant delivered by cesarean section at thirty-one weeks because of an increase in toxic signs in a patient who had had kidney damage as well as severe hypertension (blood pressure of 210 systolic, 110 diastolic) before pregnancy began. (This was the only fetal death in this series of 50 patients that was associated with superimposed toxemia.) The past obstetric histories of all these patients, however, gave good indication that the disease was sufficiently severe to endanger pregnancy. Although the use of stilbestrol should not supplant clinical judgment in the management of hypertension complicated by pregnancy, it appears, from the results presented, that its prophylactic administration to patients in whom early interruption is not indicated reduces the incidence of superimposed toxemia (thereby minimizing further damage to the vascular system) and greatly increases the chances of obtaining a living child.

TABLE 3 Sequences of Late-Pregnancy Complications in 49 Patients with Three or More Consecutive Obstetric Complications Prior to Stilbestrol Treatment *

COMPLICATION	PAST OBSTETRIC HISTORY		PREGNANCY ON STILBESTROL	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
Abortion†	53	26	2	4
Spontaneous premature delivery‡	61	29	11	22
Death from prematurity	(44 72)		(2 18)	
Stillbirth (unexplained)	26	13	2	4
Pre-eclampsia or eclampsia	50	24	4	8
Fetal loss from toxemia	(22 44)		(1 25)	
Bleeding in last trimester	13	6	1	2
None	7	3	30	61
Total living babies	56	27	42	85

*At least 2 of these occurred after 22 weeks. The total number of previous pregnancies was 201.

†At less than 22 weeks.

‡At less than 37 weeks.

weeks, any albuminuria in patients with no pre-existing renal disease or increased albuminuria in those with nephritis constituted a diagnosis of superimposed toxemia. There was a significant reduction in the incidence of this complication, from 52 to 28 per cent, and an even more striking decrease in fetal mortality—there was only 1 fetal death associated with superimposed toxemia in the pregnancies when stilbestrol was being taken, an incidence of 7 per cent, whereas 12, or 22 per cent, of their previous 55 toxic pregnancies had resulted in loss of the infant.

Finally, the past history of these patients had only 13 uncomplicated pregnancies, an incidence of 12 per cent, whereas nearly half the same patients, when given stilbestrol from early in pregnancy, delivered at term with no obstetric complications whatsoever.

The gratifying results in these 50 patients should be moderated by the explanation that only 12 of them had diastolic pressures above 100 prior to the twenty-second week, these being the only ones in whom the severity of the pre-existing disease might have made early interruption advisable. In these 12 cases there were 3 fetal deaths, 1 due to spontaneous abortion at twenty weeks, 1 to spontaneous premature delivery at twenty-six weeks and the

Sequences of Late-Pregnancy Complications

Of the 180 women to whom stilbestrol was given for the prevention of complications of late pregnancy, 49 had had 3 or more previous consecutive pregnancies that had been complicated by some abnormality associated with a deficiency of the placental steroid hormones. There were a number of abortions in the over-all past histories, but the last 3 pregnancies of each patient had included at least 2 in which complications developed after the twenty-second week. Forty-four of these women (90 per cent) had never had a full-term, uncomplicated pregnancy, although none of them had had less than 3 previous gestations and the average number was 4.3. Considering the repetitive nature of late-pregnancy complications in this group of women, it seems valid to base evaluation of stilbestrol treatment upon a comparison with their past obstetric histories. Such a comparison is presented in Table 3.

Although spontaneous abortion was markedly lowered, there was no significant reduction in the incidence of spontaneous premature delivery, possibly because patients who would have aborted without stilbestrol progressed beyond the twenty-second week, but were still unable to carry on to term. Fetal loss from prematurity, however, was reduced from 72 to 18 per cent. The factors that appear to be operative in the reduction of fetal mortality from prematurity when stilbestrol is given are discussed below.

Of the 145 fetal deaths in the previous pregnancies of these patients, 26 were accountable to unexplained stillbirths. The incidence of this abnormality was considerably reduced, from 13 per cent in the previous pregnancies to 4 per cent when stilbestrol was administered.

Twenty-three of the 49 women had had pre-eclampsia or eclampsia (2 cases) in previous pregnancies, with a total of 50 late-pregnancy toxemias

in the past obstetric histories. Fourteen women had had this complication in at least 2 consecutive pregnancies prior to the one in which stilbestrol was given. There was no eclampsia on stilbestrol. The incidence of toxemia was reduced from 24 per cent in the past obstetric histories to 8 per cent on stilbestrol, and the fetal mortality associated with this disease from 44 to 25 per cent.

A small number of the previous pregnancies of these 49 women (6 per cent) had been complicated by bleeding during the last trimester. Only one (2 per cent) had this abnormality on stilbestrol.

Finally, on stilbestrol, 30 of these women (61 per cent) went through pregnancy to term with no complications whatsoever, whereas only 7 per cent of the previous 201 pregnancies had been uncomplicated. Forty-two of them (85 per cent) gave birth to children that lived, as against only a 27 per cent fetal salvage in the past obstetric histories. Of these 49 women, all of whom had had 3 or more previous pregnancies, 17 had no living children

was 4, or 28 per cent, which is high but is a distinct improvement.

Among our records on 804 "obstetric problem cases," including the 66 referred to above, in which stilbestrol was given according to our dosage schedule for complications of early or late pregnancy, there was a total of 65 cases in which late-pregnancy toxemia was diagnosed. The 14 cases discussed above were the only ones in patients who had a previous history of toxemia, and the only fetal deaths were the 4 that occurred in these patients—an over-all fetal mortality from toxemia of 6.2 per cent. This is an impressive figure only when one considers that in all these women obstetric difficulties were anticipated and that 43 per cent of the 94 toxic pregnancies of their past obstetric histories had resulted in death of the fetus.

Spontaneous Premature Delivery

Prematurity accounts for more fetal deaths than any other single obstetric abnormality except abor-

TABLE 4 Results of Prophylactic Stilbestrol Treatment for Premature Delivery or the Basis of Past Obstetric History

NO OF PREVIOUS PREMATURE DELIVERIES	NO OF PATIENTS	NO OF PREVIOUS PREGNANCIES	PREMATURE DELIVERIES		FETAL DEATHS FROM PREMATURITY		PREMATURE DELIVERIES ON STILBESTROL		FETAL DEATHS FROM PREMATURITY ON STILBESTROL	
			NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE
1	36	56	36	65	32	89	15	41	7	47
2	22	46	44	96	32	73	15	59	5	37
3	12	41	36	83	27	75	6	50	2	33
4 or more	6	29	27	93	17	63	5	50	1	33
Totals*	76	172	143		108		37		15	
Averages				83		76		49		40

*The total of fetal deaths was 133 among 172 previous pregnancies (77%) and 15 among 76 pregnancies on stilbestrol. There were 23 abortions in the past obstetric histories and none on stilbestrol.

prior to the administration of stilbestrol. Twelve of these, or 71 per cent, now have living and well babies.

Pre-eclampsia and Eclampsia

Of the 180 women being reported, 66 had had a total of 94 toxic pregnancies prior to the one in which stilbestrol was administered. Eight of these had had eclampsia. The results of a very extensive study of toxemia by Mastboom, of Amsterdam,⁹ revealed 30 per cent and 56 per cent recurrence of toxemia after a previous eclampsia and pre-eclampsia, respectively. Accordingly, 35 of these 66 women, or 53 per cent, would have been expected to have toxemia in the pregnancy in which stilbestrol was given. Actually, only 14, or 21 per cent, had this complication—a highly significant reduction if Mastboom's figures are acceptable in this country.

In the 94 previous toxic pregnancies there were 41 fetal deaths—a mortality of 43 per cent. In the 14 toxic pregnancies that the same patients had despite stilbestrol, the fetal loss from toxemia

Of the 180 women treated for the prevention of late-pregnancy complications, 76 had a history of spontaneous premature delivery. In this category we are omitting stillbirths and premature delivery associated with toxemia. One hundred and forty-three (83 per cent) of the previous 172 fetuses had been born alive spontaneously between the twenty-second and thirty-seventh weeks, and 108 of these (76 per cent) had died of prematurity.

In Table 4 these patients are grouped according to the number of premature deliveries that they had had prior to the pregnancy in which stilbestrol was prophylactically administered. In each group there was a considerable decrease in the incidence of prematurity, but, as has been pointed out elsewhere,^{1, 7} about half the women who tend to deliver early cannot be carried to term on stilbestrol. This suggests that in half these cases the primary etiology lies in some abnormality that cannot be entirely counteracted by stilbestrol administration. We have repeatedly emphasized the reciprocal relation that exists between the vascular supply to the uterus and the secretion of the placental steroid

hormones, estrogen and progesterone Adequate vascularity depends upon adequate hormonal support, but any condition that adversely affects the blood supply to the uterus has a detrimental effect upon the production and metabolism of the placental steroid hormones An inherent hypertonicity of the uterus, for example, could readily interfere with a completely normal secretion of estrogen and progesterone even when the extra stimulation for such secretion, which we believe to be supplied by stilbestrol administration, is provided It seems probable that the tendency to deliver early can often be ascribed to some such mechanical interference with blood supply to the growing products of conception

Despite the fact that half these 76 women delivered early even when taking stilbestrol, 80 per cent of them gave birth to living and well babies, whereas less than a quarter of their previous 172 pregnancies had terminated in living children This marked improvement in fetal salvage may be accounted to the fact that along with the reduction in the incidence of premature delivery there was a considerable reduction in fetal loss from prematurity (Table 4) This is apparent in all groups regardless of the number of previous premature deliveries As clinical results have accumulated, the impression has grown that the premature babies of stilbestrol-treated mothers are exceptionally large and "rugged"

TABLE 5 Incidence of Prematurity in 1191 Patients on Stilbestrol

TYPE OF PATIENT	TOTAL NO OF CASES	INFANTS DELIVERED 14 DAYS OR MORE BEFORE TERM		INFANTS WEIGHING 2500 GM OR LESS	
		NO	PER CENTAGE	NO	PER CENTAGE
Normal primigravidas	387	46	12	11	2.8
Obstetric problem cases	804	127	16	115	13.6
Totals	1191	173		126	
Averages			14.6		10.5

for their gestational ages This impression is borne out by the following analysis of our data

Premature Babies of Stilbestrol-Treated Mothers

The definition of prematurity accepted by the American Academy of Pediatrics¹⁰ is "any infant born alive who weighs 2500 gm (5 pounds, 8 ounces) or less" In presenting our data we have purposely adhered to gestational age rather than weight, partly because the past obstetric histories often gave no information concerning weights of infants and therefore no means of comparison, and partly because so many of the prematurely born infants of stilbestrol-treated mothers weighed more than 5½ pounds To determine just what effect stilbestrol had upon babies born early, we have analyzed our data concerning all those delivered fourteen days or more before term by 1191 women (to

March 1, 1949) who took stilbestrol during pregnancy according to our dosage schedules Three hundred and eighty-seven of these were primigravidas at the Boston Lying-in Hospital, a part of a twenty-one-month study in which alternate normal primigravidas were treated so that results could be compared with a group of synchronous controls receiving the same prenatal care⁷ The other 804 patients were treated either for threatened abortion or prophylactically for the prevention of early or late obstetric complications that might have

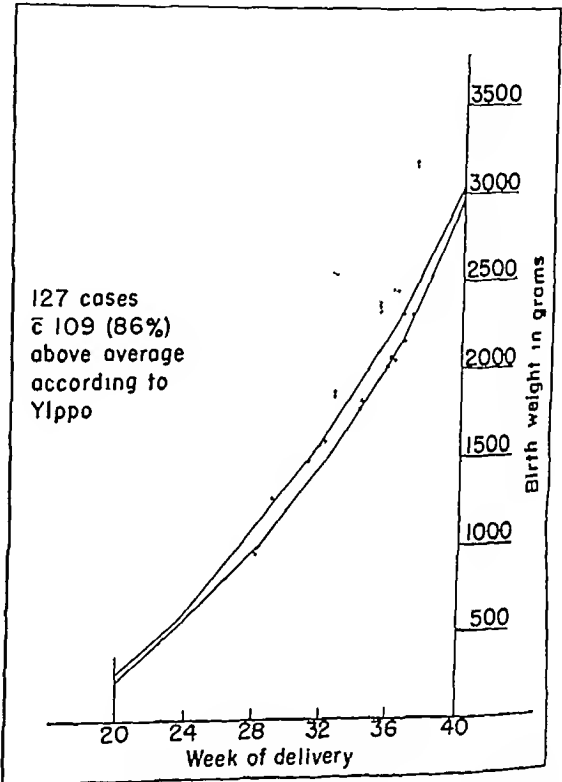


FIGURE 1 Birth Weights of Infants Born More Than Fourteen Days before Estimated Date of Confinement (Omitting Twins and Diabetic Patients)

been anticipated in view of their medical or past obstetric histories For the sake of brevity these 804 patients are termed "obstetric problem cases" All live-born infants delivered two weeks or more before term are included, whether or not the pregnancy was normal or the delivery spontaneous

In Table 5 the incidence of prematurity is presented on the basis both of dates and of birth weights In the normal primigravidas the incidence of prematurity was only 2.8 per cent according to birth weight, whereas 12 per cent were born early In the obstetric problem cases, as might be expected, the definition of prematurity had a less marked influence upon the percentage incidence, since more of these women delivered very early and had small infants That most of their babies were large for their gestational ages, however, is

shown in Fig 1 and 2, in which scattergrams for the length and weight are presented in relation to curves based on averages. The upper curve in both these charts was determined by Ylppö in 1919 and the lower by Scammon and Calkins between 1922 and 1925.¹¹ Of the 127 babies born fourteen days or more before term, 109 (86 per cent) were above average in weight. Unfortunately, accurate data on the crown-heel length were available in only 41 cases, but 37 of these (90 per cent) fell above the average curve. In the series of 387 primigravidas at the Boston Lying-in Hospital (a study being reported elsewhere⁷), over 90 per cent of the

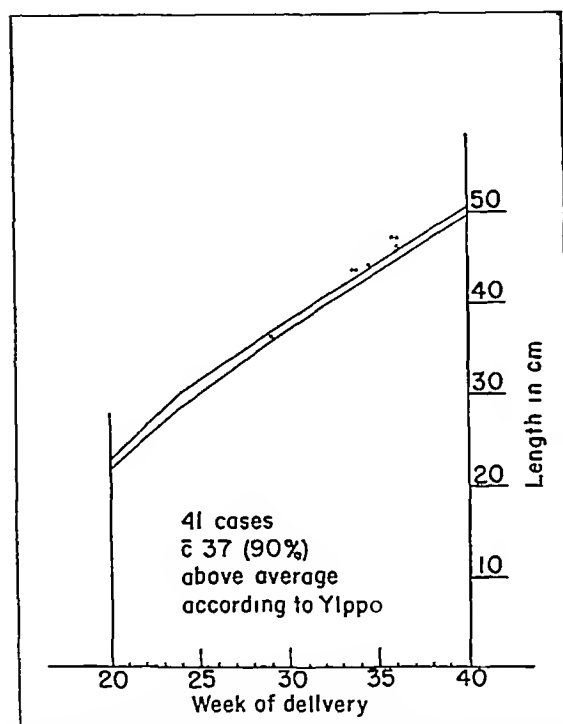


FIGURE 2 Available Information on Crown-Heel Length of Infants Born More Than Fourteen Days before Estimated Date of Confinement

41 premature infants of treated patients fell above the average curves for both weight and length, whereas in the synchronous control group of 63 premature babies of 555 primigravidas who received no stilbestrol the figure was 60 per cent. If these average curves are applicable to the present-day population, one would expect a scattergram of controls to fall 50 per cent above and 50 per cent below the lines. Sixty per cent above the average in a scattergram of 63 control cases is not a significant deviation. We may assume, therefore, that the upper curves for weight and length of Ylppö (1919) still provide a sound basis for evaluation.

This evidence for the greater size and maturity of premature babies delivered to stilbestrol-treated mothers seemed sufficient explanation for their greater chances for survival. It was of interest to discover, however, how our mortality rate in infants weighing 2500 gm. or less would compare with vital statistics on premature infants as a whole.

TABLE 6 Mortality in Premature Infants*

HOSPITAL	DATES	NO OF PREMATURE INFANTS*	MORTALITY %
Sarah Morris Hospital Chicago	1940-45	1993	25.8
Boston Lying-in Hospital	1943-45	481	15.0
Charity Hospital New Orleans	1944-45	1122	27.4
New York Hospital Pediatric Department	1943-45	506	22.3
Long Island College Hospital Brooklyn Pediatric Department	1940-45	635	16.1
Stilbestrol-treated mothers (1191 cases) — Smith and Smith dosage schedule	1943-48	126	6.3

*Weight of 2500 gm. or less

Among 1191 deliveries of stilbestrol-treated mothers there were 126 babies weighing 2500 gm (5 pounds, 8 ounces) or less. Eight of these, or 6.3 per cent, died. In Table 6 this figure is compared with similar statistics from a number of hospitals* and is shown to be very significantly lower than that of the Boston Lying-in Hospital, the lowest of the group. This could be due, of course, to fewer very small babies born to the mothers who had taken stilbestrol. That this is not the explanation, however, is shown in Table 7, in which the total fetal mortality is broken down into groups according to birth weight.

TABLE 7 Distribution of Birth and Mortality Rates in Premature Infants*

BIRTH WEIGHT	BOSTON LYING-IN HOSPITAL (1944-1948)	STILBESTROL-TREATED MOTHERS (1943-1948)
	TOTAL PREMATURE INFANTS	TOTAL PREMATURE INFANTS
gm	%	%
1000 or less	6	2.4
1001-1500	10	11.6
1501-2000	22	27.0
2001-2500	62	59.0
Totals	817	126
Averages		6.3

*Weight of 2500 gm. or less

and the results compared with similar figures from the Boston Lying-in Hospital for the years 1944-1948*. In each weight group the fetal mortality is lower than that at the Boston Lying-in Hospital. The indication is, therefore, that regardless of size, the babies of stilbestrol-treated patients are more likely to survive.

In a 1948 publication by Koch, Weymuller and James,¹² the following statement was made: "Mortality from premature birth can obviously be re-

*We are indebted to Dr. Stewart H. Clifford, associate in pediatrics, Harvard Medical School, for the vital statistics on premature infants used and for advice in analyzing our data.

duced in but two ways, either by an actual over-all reduction in the incidence of premature birth or by improvement in methods of care of the premature infant after birth." It appears from the figures presented above on the babies of stilbestrol-treated mothers that a third way of reducing fetal mortality from premature delivery should be added to this statement — namely, by improving the vascular supply to the uterus and thereby providing a better maternal environment for the fetus so that even if it is delivered prematurely it will be in better condition and actually more mature than would be expected from its gestational age. The administration of stilbestrol as a prophylactic measure appears to be one way in which this may be accomplished. Our interpretation is that even in cases in which the primary cause of premature delivery cannot be counteracted, the placental secretion of estrogen and progesterone is stimulated to its maximum capacity up to the time when non-hormonal factors gain the supremacy and bring on the vascular and hormonal deficiency associated with the onset of labor.⁶

SUMMARY

The progress and outcome of pregnancy in 180 women to whom stilbestrol was administered for the prevention of late-pregnancy complications are reported. In the evaluation of results we have relied largely upon grouping the cases in various manners so that the outcome on stilbestrol could be compared with the past obstetric histories of the same patients. All but 10 of them were multigravidas with a total of 380 previous pregnancies, only 7.5 per cent of which had been normal. Fifteen per cent of their previous pregnancies had terminated in spontaneous abortion. The other 78 per cent had been complicated by spontaneous premature delivery, unexplained stillbirth or toxemia.

Fifty women had pre-existing hypertension, either essential or secondary to renal disease. In the past obstetric histories of 105 pregnancies (no twins), there had been a 23 per cent fetal loss from spontaneous abortion and a further 30 per cent fetal loss from late-pregnancy accidents. On stilbestrol there were 3 twin pregnancies making a total of 53 fetuses. Four of these (7.5 per cent) were aborted, and another 4 (7.5 per cent) lost after the period of viability. The factors operative in the reduction in fetal mortality during later pregnancy were a lowered incidence of superimposed toxemia and of unexplained stillbirth and a decrease in fetal mortality in prematurely delivered infants.

Forty-nine patients had had a sequence of 3 or more consecutive pregnancies prior to stilbestrol in which complications associated with progesterone

deficiency had occurred. In at least 2 of the 3 the abnormalities had developed after the period of viability. Only 3 per cent of the previous 201 pregnancies had been normal, and only 27 per cent of the offspring had survived. On stilbestrol 61 per cent of patients had no obstetric complications, and 85 per cent gave birth to living children.

Sixty-six women had had pre-eclampsia or eclampsia in 94 of their previous pregnancies, with 41 fetal deaths, a mortality rate of 43 per cent from this disease. According to Mastboom, 35 of these 66 women would have been expected to have toxemia in the pregnancy in which stilbestrol was given. Actually, only 14 of them had this complication with a 28 per cent fetal mortality. Among our records on 804 "obstetric problem cases" in which stilbestrol was administered for one reason or another there were 65 toxic pregnancies including these 14. The over-all fetal mortality from toxemia on stilbestrol was 6.2 per cent, as against 43 per cent in the past obstetric histories of the same patients.

Seventy-six women had had spontaneous premature delivery in 83 per cent of their pregnancies prior to the one in which stilbestrol was given. Forty-nine per cent again delivered prematurely despite stilbestrol administration. The fetal loss, however, was reduced from 77 per cent in the past obstetric histories to 20 per cent on stilbestrol.

Analysis of our over-all data on the prematurely delivered infants of stilbestrol-treated mothers indicates that these babies are exceptionally heavy and long for their gestational ages and that, regardless of size, more of them survived than would have been expected from recent statistics on the mortality rates of premature infants.

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PITFALLS OF CHEMOTHERAPY AND ANTIBIOTICS IN SURGERY*

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ACCORDING to Webster's dictionary, a pitfall is defined as an error into which the unwary may unsuspectingly drop. By the same authority an error may be one of omission or commission. It may be stated that the pitfalls of chemotherapy and antibiotics are of two kinds: those that are liable to waylay all these agents, and those that are selective in their iniquity. Perhaps the worst error made with these remedies is to endow them as panaceas. True, they cure a few diseases all the time and others some of the time, but never all diseases all the time. The abandon with which they are prescribed, notably penicillin, for nearly every ailment under the sun, from the rectum to the ear, is astounding. So great is unwarranted faith in their infallibility that they are too often prescribed without an accurate diagnosis and detection of the causative organism.

The common error of indiscriminate use of these agents promotes three untoward and likewise common sequelae. The first is that all these chemical and biologic remedies have to some degree the insidious ability to stimulate in the organisms against which they are pitted a resistance that defeats the aim in view. There is already evidence, for example, that a new strain of a troublesome diplococcus has built up such resistance to formerly effective therapy that the drug is on its way to impotence. If an almost specific remedy can be so frustrated when wisely used, how serious it is to foster the acquisition of such resistance unnecessarily! Secondly, these remedies can sensitize persons who happen to be susceptible. This sensitization may be provoked by a small dose given unnecessarily, and may not be manifested until real need for the drug arises and then, because of the heedlessly acquired sensitivity, it cannot be tolerated. Thirdly, all these medications have untoward, and sometimes perilous, effects that can be forestalled only by careful and frequent laboratory checks too often disdained.

Another common pitfall, but of a different order, is the unwarranted assumption that the drugs can wholly replace surgery in the treatment of suppurative ailments. Admittedly, they are adjuncts and valuable ones in the handling of surgical conditions. Their proper and timely use not only often lessens the extent of necessary operation but also saves lives that surgery alone might lose. They are never, however, reliable substitutes for indicated surgery. In all fairness it should be stressed that it is not so much the drugs themselves that are beset with pitfalls as their promiscuous and ill advised use.

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More grievous perhaps are the special pitfalls peculiar to individual antibiotics and chemotherapeutic agents. Chief of the latter group are the sulfonamides. The early preparations of sulfur compounds quite often induced alarming, sometimes even fatal, untoward effects because of their high toxicity. Subsequent preparations, however, have been generally rid of toxic evils and can be prescribed with comparative safety but, especially when they are given for prolonged periods, it is still wise to check quite frequently for possible blood damage. At any rate the use of known toxic preparations can no longer be condoned. Sulfadiazine is perhaps the least toxic and has the real virtue of general effectiveness against many strains of bacteria. The newer compounds are held to be selective in action: sulfanilamide for streptococci, sulfathiazole for staphylococci and such rather insoluble compounds as sulfasuxidine, sulfaguanidine and sulfathalidine for intestinal flora, but too much faith cannot be placed in their selectivity.

It is now generally accepted that the sulfonamides act most effectively by way of the blood stream. They are still being locally applied, though their local action is slight and their local application is not without harm. On burned surfaces, for example, their absorption is uncertain and unpredictable, either too little and too slow to be useful or so great and so rapid as to become alarmingly toxic. Furthermore, since locally they become foreign bodies, they are known to delay healing, probably arousing excessive scar formation, and in the peritoneal cavity they are guilty of promoting adhesions.

The pitfalls that waylay the antibiotics are apt, because of their comparative safety, to be disregarded or forgotten. Penicillin, for example, is not always kindly tolerated. Soon after its administration such allergic reactions as urticaria, rhinitis and asthma may appear, and a few days later true dermatitis and serum sickness may occur. Even fatal anaphylactic shock has been reported.

Penicillin should be withheld until the identity of the infecting organism is established, otherwise, premature use of the antibiotic will cloud the etiologic picture. Once, however, the indication for penicillin is clear beyond peradventure, it is a grievous sin of omission to be stingy with it. Large and frequent doses are required. Even more essential is it not to stop the drug too soon. An effective blood level must be maintained until it is certain that all danger has passed. Only too often, patients who have been getting penicillin in the hospital are discharged without provision having been

made to continue it, and the omission allows disturbing symptoms of infection to recur

Streptomycin is not so generally effective as penicillin. Perhaps its outstanding virtue is in tuberculosis, against which penicillin is of no avail. Unfortunately, however, the tubercle bacillus acquires resistance to streptomycin in about six weeks on average doses. Now that pulmonary tuberculosis is safely and auspiciously attacked by surgical operation, chest surgeons have sounded a serious and timely warning not to give streptomycin to patients headed for thoracoplasty. Surgeons want to be able to count on streptomycin postoperatively to take care of any spread of the disease occasioned by operation. If a patient has already acquired preoperative resistance to streptomycin, he has forfeited a postoperative aid of great value.

As could be expected, sins of omission in chemotherapy and with antibiotics are few. Perhaps the most flagrant pitfall of the kind is failure to take full advantage of the added benefit gained by a combination of these agents. Peritonitis from appendicitis or perforated viscus, for example, is due to accumulative action of aerobes and anaerobes, which act synergistically to heighten each other's virulence. Unless penicillin, streptomycin and the

sulfonamides are energetically used, there is little chance of breaking up the synergism and overcoming the infection. In like manner, if happy outcomes are sought in such infections as carbuncles, septic hands and lymphangitis, there must be no retreat from a course of large, frequent and long-continued doses of antibiotics. Again, the mere fact that antibiotics taken orally are in some measure helpful does not warrant abandonment of the much more effective parenteral routes for the sake of sparing patients needle pricks.

Lest this paper leave an impression of pessimism and therapeutic nihilism, it should be stressed that if chemotherapeutic agents and antibiotics are regarded not as panaceas but as wondrously helpful surgical adjuncts, if they are prescribed wisely and opportunely and if their untowardnesses are constantly forestalled by the eternal vigilance that is the price of surgical success, the pitfalls that beset chemotherapy and antibiotics in surgery are easily avoided and the virtues of these agents made profitable. In the offing are more antibiotics. One and all must be studied, their limitations established, and their liabilities noted, lest they present new pitfalls to mire the unwary and lest avoidable errors be committed in their use.

MEDICAL PROGRESS

MEASURES USED IN THE PREVENTION AND TREATMENT OF CARDIAC ARRHYTHMIAS*

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THE management of cardiac arrhythmias is a common and important clinical problem. Although we shall not discuss diagnosis, it must be emphasized that accurate diagnosis of the nature of an arrhythmia is of the utmost importance since therapy useful in certain arrhythmias may be ineffective or harmful in others. In addition to reassurance, sedation, avoidance of possible precipitating factors (such as alcohol, caffeine, tobacco, emotion and exertion) and the treatment of commonly associated diseases (such as acute myocardial infarction, infections and thyrotoxicosis), specific measures affecting the rate and rhythm of the heart may be indicated. A large number of drugs and other measures have been used and are continually being recommended for

both the prevention and the treatment of cardiac arrhythmias (Table 1). It is our purpose to assemble and to analyze the available information, to indicate the order in which the various measures should be tried in an individual case, to suggest ways in which the use of available agents may be improved, to point out agents that seem particularly worthy of more extensive clinical trial, and to emphasize the criteria that are necessary in evaluation of prophylactic and therapeutic efficacy.

EVALUATION OF EFFICACY AND TOXICITY

In paroxysmal tachycardia the efficacy of a drug is measured by its ability to terminate the arrhythmia, although it is generally impossible to observe the precise instant that termination occurs. There may be little question of the association of events when the desired result is observed repeatedly after immediately effective measures such as carotid-sinus pressure and intravenous injection of acetylcholine. Several hours may elapse, however, before the arrhythmia stops after more slowly act-

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ing agents — for example, quinidine administered orally, — and the relation may not be so obvious

These considerations pertain also to the evaluation of drug toxicity, which is especially difficult in cardiac patients. Changes in the heart rate and rhythm, respiratory and central-nervous-system phenomena and various other manifestations, including sudden death, that may be due to drug toxicity may also occur in the natural course of many forms of heart disease

MEASURES AFFECTING THE PARASYMPATHETIC SYSTEM

Reflex stimulation of the vagus nerves to the heart and administration of parasympathomimetic

more, vagal stimulation by carotid-sinus pressure or eyeball pressure, for example, affects only the heart and peripheral vessels, whereas the parasympathomimetic drugs stimulate all cholinergic nerve endings to a varying degree. Side reactions that almost invariably accompany the use of drugs are rarely seen. Some form of reflex vagal stimulation, therefore, is indicated as the initial therapeutic procedure to be tried in patients with paroxysmal tachycardia

Effect on the Heart and Vessels

Vagal stimulation decreases the irritability of auricular muscle; an ectopic focus of impulse formation may be eliminated and normal sinus rhythm

TABLE 1 *Measures Used in the Prevention and Treatment of Cardiac Arrhythmias*

I. Measures affecting the parasympathetic system

A. Reflex vagal stimulation

1. Carotid sinus reflex
2. Oculocardiac reflex
3. Vomiting
 - a. Mechanical
 - b. Pharmacologic
 1. Ipecac
 2. Apomorphine
4. Miscellaneous measures
 - a. Respiratory
 1. Valsalva procedure
 2. Müller procedure
 3. Holding breath
 4. Deep breathing
 5. Irritating nasal mucosa
 - b. Postural
 1. Bending forward
 2. Stooing with head low
 3. Lying down with head low
 - c. Cold
 1. Drinking ice water
 2. Placing ice bag over precordium
 - d. Others
 1. Drawing out tongue
 2. Swallowing large bolus
 3. Pressing on abdomen

B. Parasympathomimetic drugs

1. Choline¹
2. Choline esters
 - a. Acetylcholine
 - b. Acetyl-beta methylcholine
 - c. Carbamoylcholine^{2,4}
3. Cholinesterase inhibitors
 - a. Physostigmine¹
 - b. Neostigmine
4. Pilocarpine^{1,2}

II. Quinidine (and other cinchona alkaloids)

III. Miscellaneous

- A. Digitalis glycosides
- B. Inorganic substances
 1. Magnesium ion
 2. Potassium ion¹
 3. Calcium ion¹
- C. Measures affecting the sympathetic system
 1. Adrenolytic drugs
 - a. N-dibenzyl-beta-chloro-ethylamine (Dibenzamine)^{11, 12}
 - b. Diethylamino-ethoxy-2-diphenyl (1262F)¹²
 - c. Dihydroergotamine¹³
 - d. Dihydroergocornine¹³
 2. Sympathomimetic drugs
 - a. Para-hydroxy- α -methyl-phenyl-ethylamine ('Paredrine')¹¹
 - b. Phenylephrine (Nesynephrine)¹⁴
 3. Sympathetic surgery^{11, 12}
 - a. Procaine injection
 - b. Alcohol injection
 - c. Stellate ganglionectomy
 - d. Thoracic sympathectomy
- D. Others
 1. Adenonine¹⁵
 2. Diethylaminoethanol¹
 3. Fagarine^{16, 17}
 4. Metrazol¹¹
 5. Morphine^{11, 12}
 6. Parathyroid hormone^{18, 19}
 7. Procaine^{20, 21}
 8. Quinacrine (Atabrine)^{22, 23}
 9. Veratrum vinde^{1, 24}

drugs are the most commonly used therapeutic procedures in patients with paroxysmal supraventricular tachycardia.*

REFLEX VAGAL STIMULATION

In man, reflex stimulation of the vagus nerve (Table 1), which is the simplest and safest procedure in paroxysmal supraventricular tachycardias, can be readily carried out by the physician and, with the exception of apomorphine, by the patient. After such stimulation the cardiac effect appears quickly and is of short duration. Further-

resumed. Vagal stimulation also slows the rate of the normally beating heart by an action on the sinoauricular node, and slows the rate of impulse conduction from auricle to ventricle, as a consequence, cardiac standstill nodal rhythm and partial or complete auriculoventricular block may be observed.

The sinoauricular and auriculoventricular nodes in man are each innervated by both the right and left vagus nerves. Some observers²⁵ have noted that sinoauricular asystole occurs more often with pressure on the right than on the left carotid sinus (that is, right and left vagal stimulation), whereas auriculoventricular block occurs more often with pressure on the left side. In other studies,⁴⁰ how-

*The term supraventricular as used here denotes tachycardias arising in the auricle or in the auriculoventricular node.

ever, no predominance of sinoauricular-node or auriculoventricular-node depression as a consequence of pressure on the right or left carotid sinus was seen. There is no evidence, moreover, for the superiority of either right or left reflex vagal stimulation in stopping supraventricular tachycardia. Indeed, the importance of stimulating both carotid sinuses in each case has been stressed.⁴¹ It is of interest that direct mechanical stimulation⁴² of the vagus nerve does not slow the normal heart, nor is electrical stimulation effective in persistent sinus tachycardia.⁴³

Nonidez,⁴⁴ in demonstrating parasympathetic nerve supply to the sinoauricular node, auricular muscle, auriculoventricular node and coronary vessels, found that parasympathetic nerve fibers did not appear to innervate ventricular musculature. These findings are in keeping with observations that carotid-sinus pressure usually has no effect on ventricular arrhythmias.⁴⁵⁻⁴⁷

Although vagal stimulation, by way of carotid-sinus reflexes, may induce a fall in blood pressure and a change in heart rate and in cardiac output, all affecting the coronary circulation, the exact action of vagal stimulation on the coronary arteries and coronary blood flow in man is not known.⁴⁸

METHODS OF PRODUCING REFLEX VAGAL STIMULATION

Carotid-Sinus Reflex

Anatomy The carotid sinuses are slight bulbar enlargements of the internal carotid arteries at the bifurcation of the common carotids, sometimes involving the junction of the common and the internal carotid arteries.

Physiology Variation of pressure within the carotid sinus produces prompt changes in systemic arterial pressure and heart rate, the impulses for the cardiac effects being transmitted over efferent vagus pathways.⁴⁹ Increased pressure within the carotid sinus induces reflex vagal stimulation and simultaneous inhibition of the tonus of the cardio-accelerator nerves. Although the largest accumulation of pressoreceptor fibers is in the carotid sinus, sensitive fibers are also present in the walls of the common, internal and external carotid arteries for a short distance above and below the carotid sinus.⁵⁰

Means of production Digital pressure on the carotid sinus is first performed with the patient supine, the neck extended by means of a pillow elevating the shoulders, if necessary, and the head slightly rotated away from the side of the carotid sinus to be stimulated. With the physician preferably behind the patient, one of the carotid sinuses is located. It can often be felt as an expansile body situated at the angle of the jaw, usually at the level of the thyroid cartilage, although it may be ectopic. Frequently, it is impossible to feel the actual bulbous enlargement, and one must be guided by the point of maximal carotid pulsation. The greatest

difficulty is experienced in patients with short, thick necks.

Pressure is applied toward the vertebral column by vigorously rubbing with several fingers over the carotid sinus and several centimeters above and below. Engel and Engel⁵¹ emphasized the importance of retracting the carotid artery laterally to prevent the vessel from slipping medially. The heart rate should be observed continually during the period of pressure, and, if there is any change, the pressure stopped immediately. Patients themselves not infrequently learn to terminate attacks of paroxysmal supraventricular tachycardia with carotid-sinus pressure. The duration of pressure is short, and the patients are able to recognize the termination of the attack by the cessation of symptoms. If the heart rate is not affected, pressure may be continued for approximately ten seconds. If pressure applied separately to the right and the left carotid sinuses of the recumbent patient does not stop the arrhythmia, the procedure may be more effective with the patient in the sitting position, or when pressure is applied simultaneously to both carotid sinuses.

Repetition of pressure Failure at one time during the episode of paroxysmal tachycardia of various procedures inducing reflex vagal stimulation does not preclude success with the same measures later in the attack. Several observers⁵²⁻⁵⁵ have emphasized the importance of repeating reflex vagal measures. We have had an instructive experience⁴⁴ with carotid-sinus pressure in stopping attacks of supraventricular tachycardia in a sixty-four-year-old woman with no other evidence of cardiac disease. When untreated, the attacks lasted up to thirty hours. On several occasions pressure on the right carotid sinus was followed by immediate cessation of the attack, although repeated attempts by the same observer during the previous several hours had been ineffective. This variability has been attributed⁵⁶ to differences in the degree of vagal stimulation produced at different times rather than to variation in the susceptibility of the cardiac mechanism. There is, however, insufficient evidence to explain the difference satisfactorily. From a practical point of view it is important to realize that vagal procedures should be tried repeatedly for a time before one resorts to some other form of therapy.

Influence of other agents The favorable influence of the prior administration of acetyl-beta-methylcholine,⁵⁶ neostigmine⁵⁷⁻⁵⁸ and lanatoside C⁵⁹ on the effectiveness of carotid-sinus pressure in the arrhythmias has been noted. Contrariwise, commonly used pressor agents such as epinephrine, benzedrine, paredrine and neosynephrine prevent the cardiac slowing of hyperactive carotid-sinus reflexes in patients with normal sinus rhythm.⁶⁰ However, paredrine and neosynephrine have been employed successfully in the treatment of paroxys-

mal supraventricular tachycardia. Moreover, their use may be required in the treatment of the peripheral vascular collapse observed in some cases of tachycardia.

The relations of quinidine, commonly employed in the treatment of various arrhythmias, to carotid-sinus reflex activity are of interest and importance. In animals, quinidine inhibits the cardiac effect of electrical stimulation of the vagi⁶¹ and of the parasympathomimetic drugs.⁶² Similarly, in man, Nathanson⁶³ found marked inhibition of a constantly hyperactive carotid-sinus reflex after very large doses of quinidine sulfate administered over a period of four or five days. However, the administration of quinidine in smaller but therapeutically effective doses of 0.2 to 0.6 gm. two or three times at two-hourly intervals has been shown⁶⁴ to have no effect on the activity of this cardioinhibitory reflex in 6 patients with angina pectoris. The plasma concentrations were of the magnitude usually seen after these therapeutic doses.⁶⁴

Side effects. Untoward effects such as syncope and convulsions may follow carotid-sinus pressure. These may be observed in patients who have never had a fainting spell or other symptoms suggesting a hyperactive carotid-sinus reflex. They may occur, moreover, in the absence of significant cardiac slowing.⁴⁰ Syncope and convulsions are much more apt to follow carotid-sinus pressure with the patient in the sitting or standing positions or with bilateral simultaneous pressure, they are more likely to occur in elderly patients and particularly in patients with angina pectoris. In elderly patients with generalized arteriosclerosis, prolonged carotid-sinus pressure with complete occlusion of the carotid artery may be followed by transient or permanent hemiplegia.⁶⁵ Shookhoff⁶⁶ describes the occurrence of ventricular fibrillation with cardiac recovery in association with carotid-sinus pressure in a patient with auricular fibrillation. Rarely, precordial pain, wheezing and gastrointestinal symptoms have been observed. These effects are uncommon but indicate the importance of maintaining pressure only as long as is absolutely necessary and, as mentioned above, generally not longer than ten seconds.

Efficacy in treatment of paroxysmal supraventricular tachycardia. The frequency with which carotid-sinus pressure terminates paroxysmal supraventricular tachycardia is not established. Levine⁴⁷ states that auricular tachycardia can "generally" be arrested by one of the procedures inducing reflex vagal stimulation. White,⁶⁷ however, states that reflex vagal stimulation is effective in only 10 per cent of all cases of paroxysmal tachycardia, a great majority of which are supraventricular. In 17 patients, Starr⁶⁸ found that carotid-sinus pressure alone was successful in terminating 16 of 50 attacks (32 per cent).

There is no necessary relation between pre-existent hyperactivity of the carotid-sinus reflex

and the efficacy of carotid-sinus pressure in an episode of tachycardia.

Efficacy in other arrhythmias. Carotid-sinus pressure and other means of reflex vagal stimulation are not significantly effective in other arrhythmias. Although the ventricular rate may be slowed in auricular fibrillation, normal sinus rhythm is not restored. In auricular flutter the increased auriculoventricular block produced by the reflex stimulation may slow the ventricular rate and enable the auricular deflections to be seen more readily in the electrocardiogram. Weiss and Baker⁶⁸ observed temporary change of auriculoventricular-node rhythm to normal sinus rhythm, and we have seen halving of the ventricular rate during carotid-sinus pressure in a patient with auriculoventricular-node tachycardia.

Many case reports testify to the ineffectiveness of reflex vagal stimulation in paroxysmal ventricular tachycardia.⁴⁵⁻⁴⁷ Weiss and Baker,⁶⁸ however, noted instant disappearance of paroxysmal ventricular tachycardia following carotid-sinus pressure.

Summary. Carotid-sinus pressure is a simple and relatively safe means of inducing reflex vagal activity to stop attacks of paroxysmal supraventricular tachycardia. It is the first measure to be tried in all such cases, and, if ineffective, should be repeated at frequent intervals. There are individual variations in the excitability of various vagal reflexes. The absence of an effect from carotid-sinus pressure does not exclude the possibility of a markedly active response from another means of inducing reflex vagal stimulation.

Carotid-sinus pressure has little therapeutic value in other arrhythmias.

Oculocardiac Reflex Induced by Eyeball Pressure

Physiology. In the oculocardiac reflex, afferent impulses are transmitted centrally through the ophthalmic fibers of the trigeminal nerve to connect with the vagal nuclei, where efferent inhibitory impulses are transmitted along the vagus nerve to the heart.⁶⁹ After eyeball pressure, inhibitory effects are observed on the sinoauricular node, the auricular muscle and the auriculoventricular conduction system.⁷⁰⁻⁷¹ These are similar to those seen with other types of reflex vagal stimulation. It has been stated⁷⁰ that pressure on the right eye induces a more marked effect on the sinoauricular node and the auricular muscle, whereas pressure on the left eye leads to greater effect on auriculoventricular conduction. Since the oculocardiac reflex persists during ether anesthesia even after the corneal reflex has disappeared, eyeball pressure may be utilized in the therapy of paroxysmal supraventricular tachycardia during operations.⁴⁷

As with the carotid-sinus reflex, considerable variation in the degree of activity of the oculocardiac reflex is observed from person to person,

and only occasional subjects show what may be termed a hyperactive reflex with high-grade auriculo-ventricular block, asystole and syncope. It is of some interest that hyperactive oculocardiac and hyperactive carotid-sinus reflexes occur in different types of persons and are rarely seen together.^{54, 68, 72, 73} The former is seen most often in young subjects without heart disease, and the latter is seen most often in the older age group and in people with heart disease, particularly angina pectoris. As with carotid-sinus pressure, the efficacy of ocular pressure does not depend upon a pre-existing hyperactive reflex.

Means of production The oculocardiac reflex is excited by pressure with the fingers on both closed eyes just below the supraorbital ridge, and not over the cornea. Firm pressure to the point of pain is applied and continued for twenty-five to thirty seconds. The production of pain does not appear to be a necessary part of the reflex but serves to limit the amount of pressure exerted.

Efficacy in treatment of paroxysmal supraventricular tachycardia A definite relation between eyeball pressure and the cessation of supraventricular tachycardia has been demonstrated,^{6, 47} but the data are insufficient for its efficacy to be compared with that of other methods.

Summary The oculocardiac reflex excited through eyeball pressure by patient or physician is a safe and simple means of producing reflex vagal stimulation. It is a more unpleasant procedure than carotid-sinus pressure and should be tried only after the latter has proved unsuccessful.

Induction of Vomiting

The act of vomiting is a complex phenomenon controlled by the vomiting center in the medulla. There are numerous afferent pathways so that impulses arising in various regions of the body may induce vomiting. Certain emetic agents, such as apomorphine, may act directly on the center. Efferent impulses are discharged over many parasympathetic nerves, often including the cardiac vagal fibers. The degree of cardiac inhibition does not, however, necessarily parallel the intensity of emetic action.⁵⁵ Thus, mechanical stimulation of the mucosa of the pharynx, a simple way of inducing vomiting, has often been tried in paroxysmal tachycardia, but is apparently not so effective as other emetic measures.

Ipecac Since the careful studies of Weiss and Sprague⁵⁶ ipecac has been widely used in the treatment of paroxysmal tachycardia. Each cubic centimeter of the commonly used Ipecac Syrup (U.S.P.) contains approximately 14 mg of the ether-soluble alkaloids of ipecac emetine and cephaline. These substances produce nausea and vomiting by an irritating action on the stomach, as well as by a direct action on the vomiting center.⁷⁴

Method of administration An initial dose of 4 to 8 cc is commonly employed. Nausea and vomiting usually occur within ten to forty-five minutes. If vomiting or reversion to sinus rhythm does not occur, the drug may be repeated in about forty-five minutes. In most cases successive doses should be increased until vomiting occurs, this dose, however, may still be inadequate for the re-establishment of normal rhythm. In such cases Weiss and Sprague⁵⁶ administered more than the minimal emetic dose successfully. Large doses are often followed by nausea and other evidences of parasympathetic stimulation lasting for several hours. The effective single dose varies considerably for different patients, ranging from 4 to 32 cc. Frequently, when the effective dose is established, it can be used subsequently by the patient without hospitalization or medical supervision.

Side effects After oral administration, systemic toxic effects other than weakness and diarrhea are rarely seen, probably because with vomiting the drug is quickly removed from the upper gastrointestinal tract. Weakness, hypotension, sweating, salivation and pallor may accompany the act of vomiting.

Efficacy in treatment of paroxysmal supraventricular tachycardia Successful termination of paroxysmal auricular tachycardia was accomplished in each of 14 patients studied by Weiss and Sprague.⁴⁸ Other methods of reflex vagal stimulation and acetyl-beta-methylcholine, digitalis or morphine had failed.

Summary Ipecac is of definite value in stopping paroxysmal auricular tachycardia. Its beneficial action is necessarily accompanied by vomiting and often by prolonged nausea.

Apomorphine Limited information is available⁷⁵ on the use of apomorphine in the treatment of paroxysmal tachycardia. Apomorphine produces emesis by stimulation of the vomiting center. Vomiting takes place within ten to fifteen minutes of the subcutaneous administration of 2 or 3 mg.⁷⁶ of apomorphine hydrochloride and may occur repeatedly. Central-nervous-system depression may occur, and it has been stated that "the indiscriminate use of apomorphine as an emetic cannot be too vigorously condemned."⁷⁶

In view of the possibly serious nature of the toxicity, the absence of a specific antidote and the paucity of pharmacologic data and information concerning effectiveness, the use of apomorphine in paroxysmal tachycardia does not seem warranted.

Miscellaneous Measures

Procedures inducing reflex vagal stimulation that have been mentioned as being of value in stopping supraventricular tachycardia are listed in Table 1. In the Valsalva procedure, a forced expiration is made with the glottis closed after deep inspiration. In the Müller procedure, a forced inspiration is attempted against a closed glottis after

deep expiration. We know of no data that permit an evaluation of the efficacy of these measures in stopping paroxysmal supraventricular tachycardia. It is our impression, based on our own experience and that of others, that these procedures are much less effective than other means of producing reflex vagal stimulation.

PARASYMPATHOMIMETIC DRUGS

Numerous drugs reproducing the cardiac effects of vagal stimulation have been used in the treatment of paroxysmal tachycardia, usually when reflex vagal stimulation has been ineffective. Parasympathomimetic drugs (choline, carbaminocholine, physostigmine and pilocarpine) with which there has been very limited experience (Table 1) are not discussed here.

Choline Esters

The choline esters act directly on the effector cells in tissues with cholinergic nerve supply.⁷⁶ Their cardiac effect is qualitatively similar to that of reflex vagal stimulation. The choice of a particular choline ester for use in paroxysmal tachycardia involves a consideration of the intensity and duration of the cardiac action, the intensity and duration of the undesirable side effects, the readiness with which these side effects can be controlled with atropine and the effectiveness of the drug in stopping the abnormal rhythm.

Acetylcholine Segers and his co-workers,⁷⁷⁻⁷⁸ reasoned that since experimentally induced paroxysmal tachycardia in animals can be stopped by a single induction shock, an agent that produces an intense, although transitory, cardiac inhibition might be of clinical value. Accordingly, they tested acetylcholine in the treatment of paroxysmal supraventricular tachycardia. This drug is characterized by rapid destruction and very short action in the body.

Method of administration and dose An initial dose of 20 mg (1 cc of a 2 per cent solution of acetylcholine chloride in distilled water) was injected intravenously as rapidly as possible. If the attack did not stop, the injection was repeated every three or four minutes with successive doses of 40, 60, 80 and 100 mg; the maximum single dose was 100 mg. To minimize the cerebral effects of the fall in blood pressure following acetylcholine, the drug should be injected with the patient recumbent.

Side effects and contraindications It should be emphasized, in a comparison of acetylcholine with acetyl-beta-methylcholine, that therapeutically effective doses of acetylcholine were well tolerated. Coughing, nausea, a sensation of warmth in the head and palpitation occurred, but did not last longer than a minute. Syncope was not observed and the prolonged alterations in rhythm sometimes seen after acetyl-beta-methylcholine were absent after acetylcholine.⁷⁸

The contraindications to acetylcholine are the same as those for acetyl-beta-methylcholine. Atropine sulfate is an effective antidote and a solution of 0.5-1.0 mg *should be ready in a syringe for intravenous injection before acetylcholine is given*.

Efficacy in treatment of paroxysmal supraventricular tachycardia Segers and his co-workers were able to stop 41 attacks of paroxysmal supraventricular tachycardia in 6 patients. In every case carotid-sinus pressure had been ineffective, and in some acetyl-beta-methylcholine had been without effect. The attacks stopped within thirty seconds of the effective injection of acetylcholine, the interval usually being ten to fifteen seconds. In several cases when the tachycardia recurred very soon, a second injection resulted in definite arrest of the attack. Of practical importance is the fact that the effective dose was found to remain the same for the same person in repeated attacks. Accordingly, once this amount is determined, it can be given as the first dose if the tachycardia recurs.

Similar successful therapy in 5 patients had previously been reported by Abbott,⁷⁹ using single doses of 100 mg intravenously.

Summary Acetylcholine appears to be effective in the treatment of paroxysmal supraventricular tachycardia, and its side effects appear to be less marked and of shorter duration than those of acetyl-beta-methylcholine. Further clinical trial of this drug would be of considerable interest.

Acetyl-beta-methylcholine Since the studies of Starr and his co-workers⁸⁰⁻⁸² acetyl-beta-methylcholine has become the most commonly used parasympathomimetic compound in the treatment of paroxysmal tachycardia. It is a potent, long-lasting choline ester, slowly hydrolyzed by cholinesterase and readily blocked by atropine.

Method of administration Careful observation and considerable skill are required to control the vigorous action of acetyl-beta-methylcholine. The drug is administered subcutaneously with the patient supine, to minimize the cerebral effects of the fall in blood pressure induced by the drug. An effect may be expected in one or two minutes. After subcutaneous administration, the intensity of action can be increased by massage of the injection site and decreased by the application of a tourniquet above the site. The action of acetyl-beta-methylcholine can be blocked by the intravenous injection of 0.5 to 1 mg of atropine sulfate, *the latter should be available in a syringe before the drug is administered*. Preparation for the occurrence of vomiting and involuntary defecation is advisable.

Dose The effective dose of acetyl-beta-methylcholine chloride varies from 2.5 to 60 mg, averaging about 25 mg. Young people react more vigorously to the drug than older ones, and obese persons seem to require larger doses, 10 to 20 mg may be sufficient in young patients, whereas 50 to 60 mg may be needed in older obese patients. The

initial dose of acetyl-beta-methylcholine chloride should be 5 to 15 mg, a larger dose may be given in fifteen to twenty minutes when the effects of the preceding one have worn off

Acetyl-beta-methylcholine should not be administered intravenously We have observed generalized convulsions, and syncope due to cardiac standstill has been reported,⁸² after the intravenous administration of 20 to 30 mg. If intravenous administration of atropine is not possible because of convulsions, it should be given intramuscularly

Side effects and contraindications The therapeutic effect of acetyl-beta-methylcholine on the heart is accompanied by other manifestations of parasympathetic stimulation. There may be flushing of the face and neck, generalized sweating, salivation, lacrimation, increased depth of respiration, fall in blood pressure, epigastric discomfort, nausea, vomiting and involuntary defecation. Substernal pain indistinguishable from that seen in angina pectoris has been observed. These effects are abolished by the administration of atropine sulfate. Death has been reported in several cases^{79, 83} after the administration of acetyl-beta-methylcholine, in none of these was atropine given.

The drug should not be administered to patients with bronchial asthma, angina pectoris or acute or healed myocardial infarction. Vagal stimulation in such cases may induce attacks of asthma, cardiac pain, syncope or convulsions. In patients with hyperthyroidism, acetyl-beta-methylcholine may induce auricular fibrillation.⁸⁴

Efficacy in treatment of paroxysmal supraventricular tachycardia Starr⁸⁵ reported restoration of normal sinus rhythm in 66 of 75 attacks of paroxysmal supraventricular tachycardia after one or two doses of acetyl-beta-methylcholine. Others have also reported the efficacy of this drug.⁸⁶⁻⁸⁷ In a number of cases carotid-sinus pressure, which had previously been ineffective, apparently terminated the tachycardia when applied after the administration of the drug.⁸⁸ Continued efficacy was noted in a patient with recurrent paroxysmal auricular tachycardia who received 40 injections during a twenty-month period.⁸⁶

It has been suggested⁸⁶ that, in some patients, failure of acetyl-beta-methylcholine therapy may be related to prior administration of quinidine. This, however, has not been established.

Efficacy in other arrhythmias Paroxysmal auriculoventricular-node tachycardia has been successfully treated with acetyl-beta-methylcholine⁸⁸, after various means of reflex vagal stimulation had failed, attacks were stopped within fifteen minutes in a six-year-old child in whom eight previous attacks had lasted two to fourteen days. The drug is of no therapeutic value in auricular fibrillation,⁸⁶ auricular flutter⁸⁶ or ventricular tachycardia.⁸⁹ Starr⁸⁶ reports an interesting and well controlled observation of the action of the drug subcutaneously

and by mouth in reducing the frequency of spontaneous ventricular extrasystoles. The drug also reduces the frequency of epinephrine-induced ventricular extrasystoles in man.⁹⁰

Summary Acetyl-beta-methylcholine is effective in the treatment of paroxysmal supraventricular tachycardia. Its potent action must be carefully controlled by attention to the dose, the route of administration and the rate of absorption, its antidote, atropine, should be immediately available.

Neostigmine

Neostigmine inhibits the breakdown by cholinesterase of acetylcholine formed in the body.^{90a} Its action on the heart as well as on smooth muscle and glands is abolished by atropine.

Method of administration and dose The effective dose in the treatment of paroxysmal supraventricular tachycardia is 0.5 to 1.0 mg of neostigmine methylsulfate, which may be administered subcutaneously, intramuscularly or intravenously. With intravenous injection the onset of action is very rapid, and after subcutaneous or intramuscular administration the beneficial response and maximum effect upon the cardiac rate occur within twenty minutes. Oral administration of neostigmine bromide, 15 mg three times daily, has been stated to be useful in preventing attacks of paroxysmal auricular tachycardia.⁹¹

Side effects and contraindications Mild degrees of nausea, abdominal cramps, eyelid twitching, sweating, lacrimation and salivation have been observed after the subcutaneous or intramuscular administration of 0.5 to 1 mg of neostigmine methylsulfate. This evidence of parasympathetic activity may persist for 30 to 60 minutes and is usually not so severe as to require treatment with atropine. Gastrointestinal symptoms, cramps and diarrhea have occurred after the daily oral administration of 15 to 45 mg.

Death has been reported recently⁹² in a patient given 0.5 mg of neostigmine methylsulfate intramuscularly in a test for myasthenia gravis. However, the rarity of this has been emphasized,⁹³ and the drug appears to be relatively safe even when given intravenously.

Contraindications to neostigmine are the same as those for the choline esters, and atropine is an effective antidote.

Efficacy in treatment of paroxysmal supraventricular tachycardia. Numerous observers^{2, 57, 58, 91, 94, 95} have reported the effective use of neostigmine in stopping attacks of paroxysmal supraventricular tachycardia. In many cases carotid-sinus pressure had previously been ineffective but apparently terminated the tachycardia when applied after the administration of the drug.

Summary Neostigmine is a useful and safe drug for the treatment of paroxysmal supraventricular

tachycardia The data are insufficient to compare its efficacy with that of other available agents

SUMMARY OF THE MEANS OF VAGAL STIMULATION

Reflex stimulation of the vagus nerves to the heart or pharmacologic reproduction of the effects of such stimulation are of value in the treatment of attacks of paroxysmal supraventricular tachycardia. Carotid-sinus and eyeball pressure are simple and safe means of reflex vagal stimulation. Although it is possible to obtain a parasympathomimetic effect on the heart or to potentiate reflex vagal action by means of pharmacologic agents, their use also introduces the possibility of undesirable side effects. Thus, vomiting and prolonged nausea are observed after ipecac. Acetyl-beta-methylcholine is the most widely used of the parasympathomimetic drugs, it is not at all certain, however, that other substances may not be at least as effective while causing fewer side reactions. Acetylcholine and neostigmine, particularly, should have more extensive clinical trial from this point of view.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 35411

PRESENTATION OF CASE

A fifty-year-old photographer was admitted to the hospital because of a cough and dyspnea.

Some fifteen years before entry during a routine insurance examination he was told "he had something wrong in his chest." A subsequent roentgenogram of the chest was said to show a "pus pocket" in the lower portion of the right lung. At this time he was completely asymptomatic and had no history of previous pneumonia, sinusitis, aspirated foreign bodies or oral operations. Although he continued to feel well he noticed the onset of a hacking cough one to two years after this examination. During the following ten years he suffered increasing numbers of upper-respiratory-tract infections and "chest colds." Each "chest cold" seemed to persist for a longer period than the last, and the associated cough became increasingly productive of sputum. Six years before entry he noted a rather marked change in his condition characterized by dyspnea on slight to moderate exertion. Chest colds were of one to three months' duration, with cough productive of a half to one cupful of yellowish sputum daily. Two years before admission he stopped smoking, with some subsequent decrease in cough and sputum but little change in the amount of dyspnea. Two months before entry a bronchoscopy and bronchogram at another hospital were said to have shown bronchiectasis. Following these studies he felt improved. Coughing was less, and the daily amount of sputum fell to two or three tablespoonfuls, both symptoms being more prominent in the morning. He had had no hemoptysis. Examination of the sputum for tubercle bacilli prior to admission was reported to be negative.

The past history was significant only in that he had had malaria as a child, his last chill having occurred some twenty years before admission.

Physical examination revealed an obese, middle-aged man in no distress, and was negative except for bilateral, basal inspiratory fine and medium rales most marked on the right, with decreased tactile and vocal fremitus over the right lower chest.

The blood pressure was 130 systolic, 80 diastolic. The temperature, pulse and respirations were normal.

The urine was normal. The blood hemoglobin was 15.5 gm, and the white-cell count 11,100, with 58 neutrophils. The blood nonprotein nitrogen was 31 mg and the total protein 7.0 gm per 100 cc, and the prothrombin time 17 seconds (normal, 15 seconds).

In the hospital the patient's condition remained unchanged. Two vital-capacity determinations were reported as 2.0 and 1.8 liters. A culture of the sputum disclosed abundant alpha-hemolytic streptococci, moderate numbers of *Neisseria catarrhalis* and a few nonhemolytic streptococci. An electrocardiogram was normal. A roentgenogram of the chest showed a considerable amount of mottled and linear density in the right middle lobe, with probable decrease in size of this lobe. There was some compensatory emphysema of the right lower lobe. The heart shadow was within normal limits. A roentgenogram of the nasal sinuses was normal.

On the ninth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR F DENNETTE ADAMS: On the basis of history, it seems certain that this patient had some form of chronic progressive bronchopulmonary infection. Whether it was generalized or local can be determined only by physical examination and x-ray studies. One feature in the history appears to be of no little significance: the two to three months' duration of each acute exacerbation. The usual patient with chronic bronchopulmonary infection is subject to repeated acute flare-ups, but in my experience these rarely last as long as three months. In the days prior to sulfonamides and antibiotics one occasionally encountered a single long-standing exacerbation, in recent years thanks to these new therapeutic agents, the acute attacks rarely last longer than a fortnight and are often shorter. If this is a case of recent years, it seems unlikely that the patient would not have had the benefit of the newer remedies.

DR HELEN PITTMAN: The patient left the hospital last Sunday, so it is a very recent case.

DR ADAMS: Then it seems fair to assume that at least during the past nine or ten years he must have had sulfonamide or penicillin therapy, or both. I do not see how he could have escaped it, aware as I am of the generosity with which these agents are dished out. One would suppose that if he had only bronchiectasis, chemotherapy or antibiotic therapy, perhaps supplemented by postural drain-

age, would have held his periods of incapacity, which were due to acute flare-ups, to one or two weeks or less. That these periods of acute trouble were so protracted suggests to me that there must have been an obstructive element in addition. One cannot stand on the diagnosis of bronchiectasis alone.

The physical examination is not helpful. Rales are reported in the lower lobes. On the right, tactile fremitus and vocal fremitus were diminished, but without further information, one cannot draw any conclusions. The report is inadequate. One could say that if there were dullness in this region, ventilation was poor or the pleura was thickened. If hyperresonance was found, compensatory enlargement of the lower lobe or trapped air could be postulated. The quality and intensity of the breath sounds are not mentioned. The same line of reasoning pertains there. With diminished breath sounds one would presuppose thickened pleura or trapped air, with increased breath sounds, compensatory enlargement. Incidentally, the term "compensatory emphysema" is not a good one because the word emphysema implies actual changes in the lung. In so-called compensatory emphysema, no real structural changes are present.

The laboratory examinations are of no additional help. So we now come to the x-ray studies. Will Dr. Wyman lend us a hand?

DR. STANLEY M. WYMAN: There is an area of linear, somewhat mottled density in the right-midlung field, lying rather medially. It is well seen in the lateral view extending anteriorly in the distribution of the middle lobe. There is overaeration of the right lower lobe. The pleura over the right middle lobe is definitely thickened, measuring up to 0.5 cm. The disease in the right middle lobe is well seen in this position. There is no appreciable thickening of the pleura in the right chest elsewhere. The lung fields otherwise appear essentially normal, and the heart is not remarkable. There is a congenital anomaly of the second and third ribs. The picture is quite consistent with a chronic process in the right middle lobe. I cannot see the bronchi well enough to comment on the patency in that region.

DR. ADAMS: The protocol states that there is compensatory emphysema in the right lower lobe. Can you distinguish between that and trapped air?

DR. WYMAN: One could by fluoroscopy.

DR. ADAMS: You can observe that air does not get out of the area?

DR. WYMAN: The lower lobe is diminished in size. The term "compensatory emphysema" was used because the right lower lobe was seen on fluoroscopy to aerate and decrease in size normally. Therefore, we believed that there was no occlusion of the bronchi in that region.

DR. ADAMS: You are sure of that?

DR. WYMAN: Reasonably.

DR. ADAMS: You know that the fluoroscopic note was made.

DR. WYMAN: I observed that myself.

DR. ADAMS: Then I am sure of it too.

It is perfectly obvious that there was a chronic localized process, presumably in the right middle lobe or perhaps in the lower. Unhappily, it is up to me to decide what it was. If this were straight, uncomplicated bronchiectasis, somewhere in the past history one would expect a report of a severe acute respiratory infection or one of the other episodes mentioned in the protocol. The patient recalled no inhalation of a foreign body, that does not exclude the possibility, however. Bronchiectasis due to whooping cough, influenza or other acute respiratory infection occurring in childhood would probably have developed during youth or early adult life. In such a case failure to recollect the occurrence of the disease in early childhood would not be surprising, and the history might then be regarded as unreliable. The patient was fifty years old when he came to this hospital. If the history is correct, he was approximately thirty-five when the first indications of trouble were discovered and forty when the earliest symptoms appeared. Consequently, it seems reasonable to suppose that he would have remembered any respiratory infection occurring, say, in his twenties or thirties that might have precipitated the present trouble. One must therefore add something to the diagnosis of bronchiectasis. I believe that the something-to-add is bronchial obstruction, with secondary infection and bronchiectasis distal to it. It could have been foreign body, but evidence is lacking. A tuberculous lesion of the bronchus is a possibility, but that seems unlikely. Through the years some other manifestation of tuberculosis should certainly have developed. Of the less common pulmonary infections most are generalized, not local. We need not go into the various yeast infections and others. I prefer to stick to the more common. If bronchial obstruction was present and foreign body can be excluded, the most likely diagnosis is tumor. If it was tumor, it was adenoma. Adenoma of the bronchus is slowly growing, it does cause partial obstruction with infection beyond and frequent acute exacerbations. Hemoptysis is common, if the patient had had one or more episodes of frank hemoptysis or even streaking, I would feel more secure in making this diagnosis. I see no reason to introduce bronchiogenic carcinoma, the duration was too long. On the evidence available therefore, I will make the following diagnoses: first, chronic bronchopulmonary infection, secondly, bronchial obstruction with bronchiectasis, and thirdly, the most likely cause of the obstruction, bronchial adenoma.

DR. JOHN T. QUINBY: Do you think that the vital capacity of 2.0 and 1.8 liters was incorrect?

DR. ADAMS: You think it was too low?

DR QUINBY Yes, in view of the fact that the films did not show real emphysema and that the anteroposterior diameter was fairly good. The diaphragm moved well. That is a surprising figure to me.

DR ADAMS I did not spend a lot of time thinking about vital capacity. To me, history, routine examination of the lungs and x-ray study are much more important. I would be interested to know Dr Pittman's opinion. The low capacity could be explained by the fact that when these patients get into trouble, even with relatively small lesions, they reflexly in some way reduce their vital capacity and get dyspnea out of proportion to the degree of actual lung damage.

DR WYMAN Would you consider the possibility of cholesterol pneumonitis in this case on the basis of a chronic process? You do not know that he had bronchial obstruction. The previous bronchogram may have helped, showing no block.

DR ADAMS I cannot discuss that because I do not know anything about it.

DR TRACY B MALLORY Have we had any cases with as long a duration as this?

DR WYMAN We have had some going on for several years, but I do not know about twenty years.

DR MALLORY My impression is that the duration is under five years.

DR WYMAN I am not certain.

DR ADAMS Dr Mallory, can you call on someone else to discuss Dr Wyman's question? I would like to hear about it myself. Incidentally, I suppose that bronchoscopy was done and that the findings were not put in the record.

DR PITTMAN It had been done in another city shortly before he came here.

DR ADAMS If bronchoscopy did not show a tumor, I am vulnerable. Yet often a bronchial tumor can escape the eye.

DR PITTMAN About the vital capacity, I think it was probably correct. Dr Wyman and I discussed the problem of emphysema at some length, because I was amazed when I saw the film. I went over the chest previously and there was no lateral expansion, and I could not make out the left heart border from hyperresonance.

The patient was a very swarthy person. His color was definitely on the cyanotic tint. He had three estimations of vital capacity on three different days and all in the range of 18 to 20 liters. Clinically, I thought he had severe emphysema. Dr Wyman practically sold me the idea that he did not, but he certainly did not aerate his lungs.

DR JAMES B TOWNSEND Can we be told what the recent bronchoscopy showed?

DR ADAMS It is in the record. The only one performed elsewhere showed bronchiectasis. The bronchogram showed the same. Can Dr Pittman or someone else, discuss Dr Wyman's question?

DR PITTMAN Dr Pittman cannot.

DR MALLORY Tell us what you thought when he was in the hospital before operation.

DR PITTMAN There was some difference of opinion. He was a patient of Dr Sweet's, not mine. I saw him with Dr Sweet. He was sent to Dr Sweet specifically for operation, for bronchiectasis. I saw him after admission while he was being evaluated for suitability for surgery. He had a lot of emphysema, a lot of bronchopulmonary infection, with total and irreversible change, and I was opposed to the idea of operating. The vital capacity was tremendously reduced, and he had borderline cyanosis at rest. The history was almost useless. He could not give a history. It really made no sense. What is given in the record is as good as could be obtained. No one believed that it was reliable. My opinion was, that unless he had very definite sepsis in the right middle lobe as indicated from the degree of bronchiectasis and demonstrated by the bronchograms done prior to admission, which I never did see, if he had even half a dozen alveoli in the right middle lobe working, he had better hang on to them.

DR TOWNSEND We had one bronchial adenoma going on for twelve years, and not until the fourth bronchoscopy could a piece of it be removed to make a diagnosis.

DR ADAMS Did that patient have long attacks of acute trouble?

DR TOWNSEND I do not recall. He had tremendous sepsis.

DR ADAMS If this man had two or three attacks a year and all lasted two or three months, he still would not be a rose!

DR TOWNSEND If this is collapsed middle lobe, why does the right border of the heart show that easily? It is not well defined if the middle lobe is totally collapsed.

DR WYMAN It makes a difference whether it is the anterior or posterior segment that is involved primarily. If there is a little air in the anterior medial segment the upper heart border can be seen.

CLINICAL DIAGNOSIS

Bronchiectasis

DR ADAMS'S DIAGNOSES

Chronic localized bronchopulmonary infection, right middle lobe

Partial obstruction of bronchus, with bronchiectasis

Adenoma of bronchus

ANATOMICAL DIAGNOSIS

Lipid pneumonia (paraffinoma) of right middle lobe

PATHOLOGICAL DISCUSSION

DR MALLORY At operation, a very firm, relatively spherical mass was found in the right middle

lobe It was resected When this was cut in the laboratory the consistence was very fibrous, dense, firm and described actually as woody, with a few small gritty areas of calcification in it Microscopical examination showed that the alveoli in many areas were filled with fat droplets, partly intracellular and partly extracellular — all the characteristic changes of a lipid pneumonia of the type seen following inhalation of liquid paraffin There is nothing in the past history to give any lead on that at all It is possible that thirteen years before admission, when he had chronic sinusitis, the patient used a nasal atomizer containing liquid paraffin It was quite popular at that time, but its use has almost disappeared That is the only possible lead that I can see in the history

I will ask Dr Freiman to discuss lipid pneumonia He has seen a great many cases at the Montefiore Hospital In chronic hospitals, where patients have wasting disease, and in mental hospitals, this condition is commoner than in a hospital of this character

DR DAVID FREIMAN Mineral oil, being very bland, is readily aspirated without the patient's being aware of it As Dr Mallory stated, patients with mental disease or varying degrees of dysphagia are particularly prone to aspiration of this oil taken as nose drops or by mouth for purposes of intestinal lubrication However, even patients who do not have such conditions can aspirate oil of this sort over periods quite readily, and the pulmonary picture is very characteristic The alveoli of the lung are filled with macrophages containing large droplets of liquid petrolatum that vary widely in size and displace the nucleus to one side of the cell This appearance is very different from cholesterol pneumonitis, in which the macrophages are filled with fine droplets that do not displace the nuclei The macrophages in lipid pneumonia migrate into the alveolar septums, where many of them disintegrate, releasing oil droplets A marked fibrous reaction develops around the oil, which tends to obstruct the lymphatic channels and further interferes with drainage from the sector The alveolar spaces are frequently lined by crescentic, foreign-body giant cells The stroma is at first very cellular, but as the fibrosis increases the cells tend to disappear, eventually leaving dense scar tissue in which only oil-filled spaces remain — the so-called paraffinoma This oil can be readily demonstrated with appropriate fat stains Foci of calcification are occasionally seen Since the oil tends to be aspirated in small amounts over a long period it is common to find many phases of the development of the lesion in the same case, often within a very small area

DR ADAMS Can infection occur behind this in the peripheral part of the lobe? In other words, was this an obstructive lesion?

DR MALLORY There was some bronchiectasis and some emphysema in this lobe I cannot tell about the others

Are you willing to express an opinion whether or not surgery benefited this patient?

DR PITTMAN I should doubt it very much This man had a very lengthy, stormy postoperative course acute arrhythmia, paroxysmal tachycardia (rate of 160) and probably massive collapse of the right lower lobe, requiring oxygen continuously And yet, eleven days postoperatively, when he was only able to go about an hour without oxygen, he went home, still cyanotic, still dyspneic and still requiring oxygen

CASE 35412

PRESENTATION OF CASE

A sixty-four-year-old gravedigger was admitted to the hospital complaining of shortness of breath

The patient had been seen ten years prior to admission in the Out-Patient Department, where he was treated for a hernia A chronic cough was noted at this time, but a chest x-ray film was normal Twelve months before admission the cough increased and became productive of small amounts of white phlegm Six months before admission he developed rapidly progressive dyspnea, orthopnea and poorly localized chest pain, for which he was digitalized by his physician There was also gradual deterioration of personal habits and increasing confusion that progressed to total disorientation For this reason he was brought to the Emergency Ward five months before admission Physical examination showed a plethoric, cyanotic man, with a blood pressure of 200 systolic, 90 diastolic, moderate confusion and mild left hemiplegia The veins of the neck and upper chest were dilated There were rales at both lung bases and decreased breath sounds over the right lower lobe A +++ pitting edema of both calves was noted Deep tendon reflexes were increased on the left A lumbar puncture was negative An x-ray film of the chest showed linear increased density in the left lower lobe, with a reduction in size of the lobe There was slight blunting of the left costophrenic sinus There was prominence of the heart in the region of the left ventricle and marked tortuosity and sclerosis of the aorta A barium enema was negative An electrocardiogram suggested left ventricular strain or digitalis effect The patient responded well to a low-sodium diet and diuretics or continued digitalization and returned to work, doing heavy manual labor He remained well under maintenance digitalization until two weeks prior to admission, when there was a return of dyspnea and confusion, this time accompanied by excessive perspiration, chills and fever

Physical examination showed distended veins over the neck and shoulder The trachea was in the midline There was flatness over the left lower lobe, with decreased tactile and vocal fremitus and

decreased breath sounds. The lower border of cardiac dullness was percussed 11 cm to the left of the midsternal line in the sixth interspace. The cardiac rhythm was regular, with a Grade II apical systolic murmur. The liver edge was felt 3 finger-breadths below the costal margin, and there was massive edema of the legs and genitalia.

The temperature was 104°F, the pulse 110, and the respirations 40. The blood pressure was 190 systolic, 88 diastolic.

The urine and stools were normal. Examination of the blood disclosed 11.4 gm of hemoglobin and a white-cell count of 2300, with 88 per cent neutrophils, 1 per cent large lymphocytes, 5 per cent small lymphocytes, 4 per cent monocytes and 2 per cent eosinophils, with normal platelets and hypochromic red cells. A blood Hinton test was positive, and a Wassermann reaction was doubtful. The sputum contained gram-positive cocci and gram-negative rods. Abundant alpha-hemolytic streptococci and a few *Haemophilus influenzae* were cultured from the throat. A blood culture was negative. The serum nonprotein nitrogen was 45 mg, and the total protein 6.7 gm per 100 cc, and the chloride 89 milliequiv, the sodium 128.7 milliequiv, and the potassium 5.3 milliequiv per liter.

A chest roentgenogram showed a large pleural effusion obscuring the left leaf of the diaphragm and left-lower-lung field. The heart was either considerably enlarged to the right or was displaced to the right, though the upper mediastinal structures were in the midline.

The patient was put on 200,000 units of penicillin every four hours and 6 gm of sulfadiazine a day. The temperature fell gradually to normal over the next four days, but there was no improvement in other symptoms. On the fifth day, another roentgenogram of the chest showed increase in the pleural effusion and a small amount of fluid on the right. On the seventh hospital day a left thoracentesis was done, with removal of 800 cc of red, cloudy fluid disclosing a specific gravity of 1.012. The centrifuged sediment contained 352,000 red cells and 2760 white cells per cubic millimeter. No tumor cells were found on smear, and the fluid was sterile on culture. On the following day 700 cc of similar fluid was removed. On the eighth day the temperature began to rise, reaching 103°F, and mental confusion increased. The fever persisted, and on the eleventh day there were flaccid paralysis of the left arm and spastic paralysis of the left leg, with extensor plantar response. Respirations became labored, and oxygen was administered. Late that evening a confluent purpuric rash appeared over the lower legs, forearms and flanks. An hour later the patient died quietly.

DIFFERENTIAL DIAGNOSIS

DR MARIAN W. ROPES. In this case, there are three major sites of involvement. As I see it the

problem is to determine the type of involvement in each site, if possible, and then to determine whether any or all are related, the three major sites to my mind being heart, brain and lung. To consider the heart first, the cardiac failure, which eventually was both left and right sided, occurred first six months before admission, responded to treatment and then recurred terminally. It seems probable that the etiology of the heart disease was vascular. I think there are two possible vascular diseases to be considered — namely, arteriosclerotic and hypertensive and periarteritis nodosa. It is difficult to say what part of the cardiac involvement was secondary to the pulmonary disease. I think, probably, in the terminal event this played some role, but there was underlying heart disease of some other type. In this patient, with a positive blood Hinton test, there is one other possibility that must be considered — syphilitic myocarditis. Since this is rare, and does not explain the total picture, I think that it is extremely unlikely in this case.

The second site of major involvement was the brain. Here, again, the deterioration, the confusion and the recurrent paralyses suggest that the probable cause of the brain involvement was vascular. There are three possible etiologies to be considered — arteriosclerosis, syphilis and, again, periarteritis nodosa. I think any one of these three could produce the total picture. There is at least one other possibility that must be considered in this case — namely, metastatic involvement of the brain. However, the long interval of six months, during which I judge he was completely free of symptoms, would be unusual. One might also wonder if the electrolyte disturbance, with abnormal sodium, potassium and chloride, had anything to do with the cerebral symptoms. However, they were presumably not present in the early course, and I doubt that they played a major role in the final illness. They may have been due in part to the fact that he had been on a low-sodium diet for six months.

The third site was the lung. Here, I find it difficult to determine the possible types of involvement causing symptoms. The chronic cough, which was present for ten years before admission, suggests underlying bronchial infection of some degree, and probably an infection played some role in the final illness. The chills, fever and elevation of neutrophils and the response of the fever, at least, to penicillin and sulfadiazine would be in accord with this. Tuberculosis must surely be mentioned in view of the rather long story of pulmonary involvement, but I think that with the total picture that is unlikely.

May we see the x-ray films to get some help in explaining the type of pulmonary disease?

DR JOSEPH HANDELIN. Unfortunately, I have only the films of the present illness. Those taken ten years before admission are not available, and those of the last six months were not given to me.

The films extend over an eight-day period and demonstrate homogeneous obscuration in slightly less than the lower half of the left-lung field. The heart, as said in the protocol, is either displaced to the right side or else enlarged considerably to the right. I cannot be certain. It is apparent that the mediastinum is slightly widened, superiorly. I think part of this results from the superior vena cava, which casts a shadow on the right side superiorly, and there may well be paramediastinal fluid on the left, which accounts for the widening on the other side. There is also visible slight distortion of the tracheal shadow at the thoracic inlet and just within the upper thorax. This could result from an enlarged thyroid gland, or it might possibly be due to metastatic lymph-node involvement. The aerated portion of the left lung is not unusual in appearance, except that the left hilus may be a little lower than it should be. This in turn suggests that there may be obstruction to the left lower main bronchus, with collapse of the left lower lobe, although collapse of the left lower lobe may be due to fluid accumulation alone. Precisely what is occurring, we cannot say because of the obscuring fluid. The right lung is not remarkable except for a moderate amount of fluid at the right base. The last film shows subcutaneous emphysema along the left chest wall following thoracentesis.

DR ROPES: These are helpful to me because, in addition to the fact that there was possibly slight atelectasis six months before, they suggest that there may have been more atelectasis during the terminal episode.

There are several etiologic processes that might be considered. One is syphilis, but since syphilis of the lung is very rare, and this is not a typical picture, I think it can be discarded. Whether or not vascular etiology would explain the picture, I do not know, but it must be considered in view of the evidence of vascular involvement elsewhere. Part of the picture might be explained on this basis but not the early decrease in the size of the lung, which I assume was due to atelectasis. In addition, the bloody effusion could not be explained on such a basis. Pulmonary infarct must be thought of in view of the rather sudden onset of the terminal illness and the bloody pleural effusion. Again, this does not explain the preceding pulmonary disease. I believe that the change in cough that occurred a year before admission and the x-ray changes present six months before admission, suggesting at least atelectasis, the bloody effusion, and probably more collapse of the lower lobe, with the possibility now of even metastatic areas in the mediastinum, are strongly suggestive of tumor.

Having considered the three sites, the question is to decide whether the three involvements can be due to the same process. I think only two possibilities would have to be considered: periarteritis nodosa and syphilis. Periarteritis nodosa can ex-

plain the cardiac and cerebral involvement but, as I have already said, would not to my mind explain the entire pulmonary picture. Syphilis would explain the cerebral picture but probably could not explain either the cardiac or the pulmonary condition. So I think that I must make at least two diagnoses. Of the pulmonary possibilities I would choose tumor as perhaps the most likely. Lymphoma is suggested definitely by the bloody effusion, but the age and probably the type of progression, with early atelectasis, would be against it and would make carcinoma slightly more likely. The cardiac and cerebral involvement were on a vascular basis, presumably arteriosclerotic, although I cannot rule out the possibility that syphilis played a role in the cerebral involvement.

DR TRACY B. MALLORY: I wonder if anyone can tell about the opinion on the wards.

DR J. W. LITTLEFIELD: We believed that the bloody effusion could be due either to carcinoma or to tuberculosis of the lung.

DR HELEN S. PITTMAN: We have a case not yet proved in which bloody effusion was secondary to an intercurrent respiratory-tract infection, not tuberculosis. It seems to be that because it completely disappeared and remained so for a year, and that is fairly good evidence of it. I wondered if the culture of *H. influenzae* from the throat may have been more important than a passing finding.

CLINICAL DIAGNOSIS

Carcinoma of lung, with cerebral metastases?

DR ROPES'S DIAGNOSES

Cerebral arteriosclerosis
Arteriosclerotic heart disease
Pulmonary tumor, carcinoma?

ANATOMICAL DIAGNOSES

Hemorrhagic pericarditis, subacute
Allergic purpura
Acute glomerulonephritis
Arteriosclerosis, aortic, coronary and cerebral, severe
Hypertrophy of heart
Nephrosclerosis, chronic
Cerebral infarctions, multiple small

PATHOLOGICAL DISCUSSION

DR MALLORY: Our autopsy findings were rather surprising. They do not seem to fit into any recognizable, nameable picture, however. There was severe arteriosclerosis in numerous parts of the body. The aorta was extremely sclerotic. The coronary arteries were pipestem in character and narrow. The renal arteries were extremely narrow, both major and intranephric branches. It was noted that the vessels at the base of the brain and circle of Willis were likewise sclerotic. The surprise

of the autopsy was the finding of a very massive, hemorrhagic pericarditis. Four hundred cubic centimeters of hemorrhagic fluid was present, and the pericardium measured 4 mm in thickness and was covered with shaggy exudate. The process had been going on for a long time, since there was a great deal of fibrous thickening of the pericardial wall. Exudate was also present in the left pleural cavity but was not hemorrhagic in character.

Another surprise was provided by the microscopical examination of the kidneys, which showed, besides old lesions obviously based on arteriosclerosis and consistent with some degree of chronic hypertension, a terminal acute glomerulonephritis, which had not lasted more than a period of five or six days. The single nonprotein nitrogen taken was only 47 mg per 100 cc, a few days before death. The combination of pericarditis and nephritis is, of course, a common one, but ordinarily the pericarditis is a uremic manifestation of the terminal stages of nephritis, whereas here, it is obvious that the pericarditis long antedated the terminal period. We found a few small areas of softening of brain, all fresh. Nothing was discovered to explain the terminal paralysis, but perhaps further study of the brain will bring something out. The skin lesions showed extremely intense polymorphonuclear infiltration—enough almost to suggest sepsis, but Dr. Walter Lever has been over the sections and points out that in certain allergic forms of purpura very marked leukocytic infiltration may occur, so marked that the hemorrhage is almost obscured by purulent infiltration. A very careful search through a great many sections failed to show any lesions that would permit a diagnosis of periarteritis nodosa, which would be about the only reasonable way of tying these factors together. We have no such evidence, however, and I think we have enough sections to rule it out. I cannot fit the picture into any of the "group" diseases, and all I can do is list the various findings.

DR RICHARD CLARK Was an electrocardiogram taken in the second entry? Was there anything different from the first entry?

DR LITTLEFIELD I believe no electrocardiogram was taken.

DR MALLORY No significant degree of fibrosis of the myocardium was noted.

DR ALFRED KRANES Was the heart enlarged?

DR MALLORY The recorded weight was 600 gm, partly because of the shaggy, fibrinous pericardial exudate, perhaps 500 gm was the actual heart weight.

DR KRANES Was the enlargement confined to any chamber?

DR MALLORY No, there was diffuse enlargement of all chambers. The lungs showed chronic bronchitis and a moderate grade of old bullous emphysema that we thought was past history and contributed nothing at all to the terminal diagnosis.

DR HANELIN What was the explanation for the bloody thoracentesis?

DR MALLORY It is possible that they tapped the pericardium. Small amounts of fluid were found in both pleural cavities, about 50 cc on each side. This was blood stained, but there was no evidence of pleuritis and it was believed the blood was introduced during the course of the autopsy. The fluid in the pericardial sac was frankly bloody. I think the pericardial effusion would very adequately explain the enlargement of the heart to the right in the roentgenogram. It is the only possible lead.

A PHYSICIAN What was the lesion by x-ray study in retrospect?

DR HANELIN In retrospect the abnormal placement of the heart in the right thorax was due to the enlarged heart and the pericardial effusion. The uniform increased density of the left lower chest resulted from the cardiac enlargement and the pericardial and left pleural effusion.

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would constitute a calamity, and much of the justly earned prestige of the Army Medical Library would dwindle and the Library would become merely a large local collection of material to be consulted in Washington.

Washington is the logical place for a distribution center for medical literature, and the Government should in the interests of public health and welfare provide the necessary support for these publications.

COMMUNITY HOUSE

METROPOLITAN Boston's United Community Services are to have a permanent home, the final posthumous benefaction of two charitable sisters, Ellen F. and Ida M. Mason. These public-spirited Boston ladies, who lived at the corner of Walnut and Beacon streets in the house that is now the headquarters of the Judge Baker Guidance Center, left, in the disposition of their property, nearly a million dollars to philanthropy. Half this sum was given directly to various health, social and educational institutions in Boston, Newport and the South, the remainder was established in 1929 as the Mason Fund, the income of which was to be distributed to charitable organizations and the principal of which after 1942, might be disposed of in the same way.

This final distribution is about to be effected by the purchase of the present twelve-story building of the Boston City Club, also on Boston's Beacon Hill, for the use of the red-feather organization and other social agencies. Boston, rarely backward in charitable enterprises but often slow in the development of material facilities, will thus acquire a general "community building" as other cities of comparable size possess.

The purchase of this center comes at a propitious moment, only three months after the establishment of United Community Services as a reorganization of Greater Boston's welfare agencies resulting from the Greater Boston Community Survey.

In announcing the transaction emphasis is placed on the fact that the gift of the Mason Fund represents a separate grant for this housing project.

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FIRST THINGS FIRST

THE report of the recent Greater Boston Community Survey contained a protest that was not the first to be voiced against the presence of those unco-ordinated fund-raising activities that constitute such a threat to the basic essential services of a community. The complaint has become almost universal that the national power drives, appealing to the emotions of a still generous people, are cutting across the supply lines of the vital locally organized services of all major communities and are threatening their continued existence.

Nor is it only the March of Dimes, the National Tuberculosis League, the American Heart Association, the American Cancer Society, the American National Red Cross and other nationally recognized organizations that are in this fashion and certainly with the best of intentions tapping in on the re-

sources of each community. The number of worthy appeals has grown to the point where rarely is there a moment in which one or more is not in existence, and the now well publicized plea of the community that begged for a "leave us alone week" gains added sympathy.

Basil O'Connor, former president of the American Red Cross—a supercolossal and particularly independent organization—took it upon himself to bring into the open the danger that now threatens the future of all voluntary health and welfare agencies. In his address before the Annual Convention of the Red Cross in June he indicated plainly that compulsion under state control may yet supersede "voluntary association for the alleviation of human suffering."

Such a change in method is actually not at all unlikely to take place even in this country, as it pursues its course toward the condition of a welfare state. The outcome can only be hastened by the nonco-operation of the fund-raising organizations that ignore the equal if not the prior rights of those charities that begin at home.

As the *Journal of the American Medical Association* remarks, in commenting editorially on Mr. O'Connor's speech:

If this nation were to remove from the sphere of voluntary action the whole experience of relief and assistance and transform it into "a massive, mechanical system of invisible deductions and automatic contributions," people would be deprived of the individual exercise of the impulse of generosity.

And yet that is exactly the situation into which the excessive and unco-ordinated demands of a variety of agencies are leading the country in their zeal.

No more than two intensive campaigns should be tolerated by the people of any community. These should be a community-fund drive at one time of year for the local health and welfare organizations, and as remote from this as possible in point of time a combined drive for all the other health and relief agencies.

When the fact is fully appreciated that last year, in addition to the Community Fund drive, ten organized campaigns sought \$12,000,000 in Metropolitan Boston, the statement made in the Survey report may be heeded: "Responsibility

rests with the community leaders who sponsor, support and give direction to these miscellaneous campaigns. When they wish correction they can bring it about."

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and that none of the money raised by the Community Fund's annual campaign is being used in the purchase of the building

CONGRESSES IN SURGERY

THE clinical congress of the American College of Surgeons, to be held in Chicago from October 17 to 21, is of great interest not only because this is the thirty-fifth such congress but also because the program will include the meeting of the Sixth Inter-American Congress of Surgery—the first time the Congress has been held in the United States. The delegates of the latter organization will attend the sessions of the College and will hold their own meetings from October 21 to 23. Headquarters for both congresses will be at the Stevens Hotel.

The program of the College will include the fourth Martin Memorial Lecture, delivered by Sir James R. Learmonth, of Edinburgh, at the Presidential Meeting on October 17. Lord Webb Johnson, of London, president of the Royal College of Surgeons of England, will deliver the Fellowship Address at the Convocation on October 21, when fellowship will be conferred upon several hundred initiates. Operations will be presented in color over television from St. Luke's Hospital during the Congress. The other events will include scientific sessions, official meetings, medical motion pictures, technical and scientific exhibitions and operative and nonoperative clinics in 24 hospitals in the Chicago area.

Between two and three hundred Latin American surgeons are expected to attend the Inter-American Congress, which is also open to fellows from the United States and Canada. The sessions will center around three main subjects: "Acute Cranio-cerebral Trauma," with Dr. E. Jefferson Browder, of Brooklyn, as the main speaker; "Treatment of Injuries in the Region of the Ankle with Complications and Sequelae," with Dr. Harrison L. McLaughlin, of New York City, as the main speaker; and "Pulmonary Carcinoma" with Dr. Evarts A. Graham, of St. Louis, as the main speaker.

The programs of both congresses offer material of interest to all surgeons. The international character of the occasion makes it of particular significance to all who are concerned with medical and surgical care in the United States and abroad.

Andrew H. Brand, 14 years of age, is on exhibition at Louisville, Ky. He weighs 500 pounds, is 5 feet 6 inches tall, 6 feet round the waist and 3½ round the thigh.

Boston M. & S. J., October 10, 1949

MASSACHUSETTS MEDICAL SOCIETY



DEATHS

ADRIANCE — Vanderpoel Adriance, M.D., of Wills-town, died recently. He was in his eightieth year. Dr. Adriance received his degree from Columbia University College of Physicians and Surgeons in 1893. His widow, two sons and a brother survive.

ROLFE — William A. Rolfe, M.D., of Boston, died on September 24. He was in his eightieth year. Dr. Rolfe received his degree from Harvard Medical School in 1890. He was a member of the American Proctologic Society and a fellow of the American Medical Association. His widow survives.

ROWLAND — William D. Rowland, M.D., of Newton, died on July 1. He was in his seventieth year. Dr. Rowland received his degree from University of Michigan Homeopathic Medical School in 1911. He was chief of the eye staff of the Massachusetts Memorial Hospitals from 1925 to 1942. He was professor emeritus of ophthalmology at Boston University School of Medicine and was a member of the American Academy of Ophthalmology and Oto-Laryngology and the New England Ophthalmological Society and a fellow of the American College of Surgeons and the American Medical Association. His widow, a daughter, two brothers and three sisters survive.

ROYAL — Herbert B. Royal, M.D., of Harvard, died on September 14. He was in his eighty-seventh year. Dr. Royal received his degree from Bowdoin Medical School in 1887. He was formerly a member of the staffs of hospitals in Clinton, Concord and Ayer. Two sons survive.

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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1949

RÉSUMÉ

DISEASES	AUGUST 1949	AUGUST 1948	SEVEN YEAR MEDIAN
Chancroid	1	4	2*
Chicken pox	222	163	123
Diphtheria	26	17	12
Dog bite	1284	1184	1025
Dysentery bacillary	1	11	12
German measles	117	47	47
Gonorrhea	258	334	374
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	2	1*
Malaria	1	1	11
Measles	151	595	296
Meningitis meningococcal	5	7	7
Meningitis Pfeiffer bacillus	0	1	0
Meningitis pneumococcal	1	0	0
Meningitis staphylococcal	0	0	0
Meningitis streptococcal	0	0	4
Meningitis, undetermined	6	6	271
Mumps	275	428	68
Polio myelitis	725	68	72
Salmonellosis	74	12	77
Scarlet fever	66	74	157
Syphilis	153	166	210
Tuberculosis pulmonary	236	275	233
Tuberculosis other forms	8	14	15
Typhoid fever	3	2	5
Undulant fever	2	2	5
Whooping cough	479	209	475

*Five-year median

COMMENT

Diseases above the seven-year median were chicken pox, diphtheria, dog bite, German measles, poliomyelitis and salmonellosis.

Diseases below the seven-year median were bacillary dysentery, malaria, measles, scarlet fever, typhoid fever and undulant fever.

Poliomyelitis reached the highest level ever reported for the month, partly owing to the early seasonal rise in the disease. The proportion of nonparalytic cases is higher than that in any previous epidemic year.

Dog bite reached the highest level recorded for August (1284 cases) but was less than in May and June of this year (1472 and 1644).

Diphtheria was at the highest level for August since 1934.

For the third consecutive month, only 1 case of bacillary dysentery was reported.

Scarlet fever dropped to the lowest level ever recorded for the month of August.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Berkley, 2, Boston, 13, Charlton, 2, Gloucester, 2, Milford, 2, Revere, 2, Somerville, 1, Wakefield, 1, Wellesley, 1, total, 26.

Dysentery, bacillary, was reported from Lowell, 1, total, 1.

Encephalitis, infectious, was reported from Salem, 1, total, 1.

Infections hepatitis was reported from Foxboro, 1, Lowell, 1, Methuen, 1, Worcester, 1, Wrentham, 1, total, 5
Lymphocytic chomeningitis was reported from Fall River, 1, total, 1

Malana was reported from Boston, 1, total, 1
Meningitis, meningococcal, was reported from Boston, 1, Foxboro, 1, Malden, 1, Wellesley, 1, Weymouth, 1, total, 5
Meningitis, pneumococcal, was reported from Sandwich, 1, total, 1

Meningitis, undetermined, was reported from Cambridge, 1, Fall River, 1, Foxboro, 1, North Attleboro, 1, Salem, 1, Stockbridge, 1, total, 6

Poliomyelitis was reported from Abington, 4, Amesbury, 1, Andover, 2, Arlington, 13, Ashby, 1, Attleboro, 3, Anhnrrn, 3, Barnstable, 3, Barre, 1, Bedford, 1, Belmont, 5, Berlin, 1, Beverly, 1, Billenca, 2, Blackstone, 1, Boston, 127, Bourne, 3, Bovlston, 1, Braintree, 2, Bridgewater, 1, Brimfield, 1, Brockton, 12, Brookline, 8, Burlington, 1, Cambridge, 18, Canton, 2, Chelsea, 5, Chicopee, 3, Clinton, 2, Cohasset, 1, Dalton, 1, Dartmouth, 1, Dedham, 12, Dennis, 2, East Bridgewater, 1, East Longmeadow, 1, Everett, 12, Fairhaven, 1, Fall River, 2, Falmouth, 3, Fitchburg, 2, Foxboro, 2, Framingham, 2, Gardner, 2, Georgetown, 1, Grafton, 3, Greenfield, 2, Halifax, 1, Hamilton, 1, Harvard, 1, Haverhill, 4, Hingham, 3, Holliston, 1, Holyoke, 6, Hudson, 4, Hull, 2, Ipswich, 1, Lancaster, 2, Lawrence, 2, Lee, 1, Leicester, 1, Leominster, 6, Lexington, 1, Lincoln, 1, Lowell, 3, Lynn, 25, Lynnfield, 2, Malden, 23, Manchester, 2, Mansfield, 2, Marblehead, 3, Marion, 2, Marlboro, 2, Marshfield, 4, Maynard, 1, Medford, 21, Melrose, 3, Middleton, 2, Mills, 1, Milton, 8, Montague, 1, Natick, 4, Needham, 3, New Bedford, 1, Newburyport, 3, Newton, 24, Norfolk, 1, North Adams, 1, North Attleboro, 3, Northampton, 1, Northboro, 1, Northbridge, 1, Norwood, 11, Peabody, 1, Pembroke, 1, Pittsfield, 3, Plainville, 2, Plymouth, 1, Provincetown, 1, Quincy, 27, Randolph, 1, Raynham, 1, Reading, 1, Rehoboth, 1, Revere, 6, Rochester, 1, Rockland, 2, Rockport, 2, Salem, 7, Salisbury, 2, Sandisfield, 1, Sandwich, 1, Sangus, 3, Scituate, 1, Sharon, 4, Shirley, 1, Somerset, 1, Somerville, 31, South Hadley, 1, Spencer, 1, Springfield, 14, Stoneham, 1, Stoughton, 3, Swampscott, 3, Taunton, 1, Templeton, 1, Tewksbury, 2, Townsend, 1, Truro, 2, Uxbridge, 4, Wakefield, 2, Walpole, 3, Waltham, 11, Ware, 3, Wareham, 3, Watertown, 9, Wayland, 3, Webster, 1, Wellesley, 2, West Newbury, 1, West Springfield, 3, Westboro, 4, Weston, 1, Weymouth, 9, Whitman, 3, Wilbraham, 1, Williamstown, 1, Wilmington, 2, Winchester, 4, Winthrop, 14, Woburn, 8, Worcester, 17, Wrentham, 3, Franklin, 4, total, 725

Salmonellosis was reported from Boston, 4, Brookline, 67, Fall River, 1, Holyoke, 1, Lawrence, 1, total, 74

Septic sore throat was reported from Boston, 4, Free-town, 1, Worcester, 1, total, 6

Tetanus was reported from Duxbury, 1, Quincy, 1, Rockport, 1, total, 3

Trachoma was reported from Boston, 1, total, 1

Typhoid fever was reported from Boston, 1, Haverhill, 1, Middleboro, 1, total, 3

Undulant fever was reported from Millbury, 1, Watertown, 1, total, 2

CORRESPONDENCE

DIVERGENT VIEWS

To the Editor Dr. McManamy's letter in the September 1 issue of the *Journal* is interesting because the very finality with which it disposed of problems pertaining to the every-day practice of medicine paradoxically emphasizes the need of their further consideration.

For instance, should physicians who daily make or avoid decisions pertaining to life and death, happiness and suffering, absolve themselves from professional responsibilities by unquestioningly accepting a judgment pronounced with a totalitarian authority that accords neither with the spirit of science nor with democracy or Christian tolerance? Or is drawing from our minds curtains woven from dogma foreign to our American tradition of individual responsibility essential to the ideals of a profession whose function is to ameliorate human suffering by its knowledge of natural law. In stating that we "give lip service to God as the creator of life" while "we presume to usurp His authority over life,

its beginning, its functions and its end," Dr. McManamy dogmatically prescribes limitations to physicians' services without defining the line between usurpation of God's authority over life and death and service to God and humanity in preventing death and suffering. Under which category is the provision of oxygen to the newborn infant, of penicillin to the young person with pneumonia or of digitalis to the patient with cardiac disease? Must doctors forego their science for Christian Science? Or what physician, who witnesses the suffering of a patient ordained by God to die, can say that withholding the medication that permits a painless passing to eternal sleep is "murder in the first degree"? When we as obstetricians and pediatricians ponder preventing the death of a child who would die but for our efforts and in living will be a burden to family and society, are we usurping God's authority or with intelligent humility serving His will as best we may? Who can say whether Dr. McManamy's freedom from such doubts is as Christian as it is conducive to her peace of mind in avoiding difficult problems by conveniently ascribing them to God's will. Surely this is not good Catholicism.

Finally, must we physicians adopt the almost morbid "idea that the insane and feeble-minded, the sick and the weak offer us a means of working out our salvation" instead of the Christian concept that their misfortune presents a challenge to us to prevent and alleviate suffering? Will religious fervor, like antivivisection sentiment, inhibit physicians in their service to humanity, or will it join with science in enabling us by applying faithfully our ever-expanding knowledge of prevention and curative medicine to extend happiness and lessen suffering?

ALLAN M. BUTLER, M.D.

Massachusetts General Hospital

To the Editor Regarding the letter entitled "First Principles" in the September 1 issue of the *Journal*, a first principle is beware the babble of a bigot. There is no logical basis to the statement that planned parenthood is a euphemistic name for prostitution of marriage.

Let Dr. McManamy practice what she may, but advise her to cast no stones. I, for one, would not use the epithet prostitute lightly.

GEORGE M. BARTOL, M.D.

Milton, Massachusetts

To the Editor For some years I have enjoyed thoroughly the many interesting papers published in your excellent journal. I think one of the most far-reaching and provocative ones in some time is the one in the July 14 issue by Dr. Leo Alexander — "Medical Science under Dictatorship." I think his warnings that we in this country are tempted at times to slide insidiously and perhaps unconsciously into some of the potentially dangerous channels that led to the downfall of German medicine are most timely. I have been much interested in the correspondence called forth by Dr. Alexander's article. Unfortunately, the Spanish Inquisition has been dragged into this discussion. This seems to be as irrelevant as efforts to relate the issue to the burning of Salem witches. On the other hand, the recent letter by Dr. Margaret C. McManamy seems to state the issue rather clearly. I shall not waste time or space repeating her thoughts but merely point out that her discussion of first principles impresses me as a very clear statement to those who wish to build a society on God's immutable laws rather than upon the shifting sands of expediency and convenience.

HORST A. AGERTY, M.D.

Philadelphia, Pennsylvania

NOTICES

ANNOUNCEMENTS

Dr. Irving L. Pavio announces the removal of his office for the practice of ophthalmology to 520 Beacon Street, Boston.

HAMPDEN DISTRICT MEDICAL SOCIETY

A meeting of the Hampden District Medical Society will be held at Classical High School, Springfield, on Tuesday, October 25, at 8:15 p.m. Dr. Shields Warren will speak on the subject "Atomic Energy in War and Peace."

HYDE, ROBERT WELLS, 74 Fenwood Road, Boston
University of Vermont College of Medicine, 1935

JAKES, WILLIAM EVERETT, 300 Longwood Avenue, Boston
McGill University School of Medicine, 1942

JUDSON, WALTER EMERY, 65 East Newton Street, Boston
Johns Hopkins University School of Medicine, 1942

KENNEY, JAMES FRANCIS, 74 East Newton Street, Boston
Boston University School of Medicine, 1945

KULKA, JOHANNES PETER, 44 South Russell Street, Boston
Johns Hopkins University School of Medicine, 1944

KURLAND, GEORGE STANLEY, 330 Brookline Avenue, Boston
Harvard Medical School, 1943

LATORELLA, JOHN, 117 Bartlett Road, Winthrop
Middlesex University School of Medicine, 1936 Sponsor
A Paul DerHagopian, 39 Cary Avenue, Chelsea

LONGINO, LUTHER A., 300 Longwood Avenue, Boston
University of Arkansas School of Medicine, 1935

MAGILL, HERBERT KELVIN, 128 Chestnut Street, Boston
University of Colorado School of Medicine, 1937

MARNOY, SHERWOOD, 90 Orange Street, Chelsea
Middlesex University School of Medicine, 1943 Sponsor
Lawrence J. McCarthy, 520 Commonwealth Avenue, Boston

MILLER, HARRY HEYBURN, 367 Central Street, Auburndale
Harvard Medical School, 1941

MIXTER, CHARLES GALLOUPE, JR., 43 Hedge Road, Brookline
Harvard Medical School, 1939

NABETH, DONALD CLARK, Boston City Hospital, Boston
Harvard Medical School, 1942

O'BRIEN, FREDERICK WILLIAM, JR., Damon Road, North Scituate
Tufts College Medical School, 1946

OPPENHEIM, DAVID J., 14 Buswell Street, Boston
Tufts College Medical School, 1947

PALERMO, JOSEPH JOHN, 20 Crescent Avenue, Revere
Middlesex University School of Medicine, 1942 Sponsor
A Paul DerHagopian, 39 Cary Avenue, Chelsea

POSIN, HERBERT ISRAEL, 24 Lynde Street, Boston
Boston University School of Medicine, 1945

RAVVEN, ROBERT M., 74 Fenwood Road, Boston
Harvard Medical School, 1943

RODKEY, GRANT V., 16 Poplar Place, Boston
Harvard Medical School, 1943

SACK, THEODORE, 386 Longwood Avenue, Boston
Harvard Medical School, 1942

UPTON, LESLIE, 55 Park Drive, Boston
Middlesex University School of Medicine, 1942 Sponsor
David B. Stearns, 416 Marlboro Street, Boston

WILLIAMS, ALBERT HAROLD, 926 Manor Road, Alexandria, Virginia
College of Physicians and Surgeons, Boston, 1939 Sponsor
Harry Silverman, 137 Shirley Avenue, Revere
Charles G. Shedd, *Secretary*
1180 Beacon Street, Brookline

WORCESTER

ANDERSON, PAUL O., 122 Whitmarsh Avenue, Worcester
Boston University School of Medicine, 1943

CENNI, LOUIS J., 47 Saxon Road, Worcester
Temple University School of Medicine, 1943

CHURCH, RICHARD EATON, 117 Elm Street, Millbury
Tufts College Medical School, 1945

KELLY, HARRY J., 1 Midland Street, Worcester
University of Vermont College of Medicine, 1945

RICE, WILLARD GARDNER, 67-09B 186th Lane, Flushing, New York
Tufts College Medical School, 1944

SMITH, JOSEPH ROY, 467 Park Avenue, Worcester
Columbia University College of Physicians and Surgeons, 1943

WALL, ROSCOE LEGRAND, JR., 13 Zenith Drive, Worcester
Jefferson Medical College, 1940
Donald Hight, *Secretary*
57 Cedar Street, Worcester

WORCESTER NORTH

ALOIA, ANTHONY FRANCIS, 69 West Street, Leominster
Boston University School of Medicine, 1946

CHURCHVILLE, LAWRENCE ALOYSIUS, Main Street, Townsend
Kansas City University of Physicians and Surgeons, 1942
Sponsor George P. Keaveny, 62 Fox Street, Fitchburg

GOLDFARB, ABRAHAM, Oak Street, Townsend
Midwest Medical College, 1935 Sponsor Clifford S. Lancey, West Townsend

MAGEE, LINCOLN J., 323 Spring Street, Winchendon
Kansas City University of Physicians and Surgeons, 1942
Sponsor Alton B. Skelton, 89 Central Street, Winchendon

SOLDINI, ENRICO CELESTE, 62 Day Street, Fitchburg
University of Vermont College of Medicine, 1912

STONE, ANTHONY JOSEPH, 468 Chestnut Street, Athol
Yale University School of Medicine, 1944
J. G. Simmons, *Secretary*
30 Myrtle Avenue, Fitchburg

MASSACHUSETTS DEPARTMENT
OF PUBLIC HEALTHCOMMUNICABLE DISEASES IN MASSACHUSETTS
FOR AUGUST, 1949

RÉSUMÉ

DISEASE	AUGUST 1949	AUGUST 1948	SEVEN YEAR MEDIAN
Chancroid	1	4	2*
Chicken pox	222	163	123
Diphtheria	26	17	12
Dog bite	1284	1184	1025
Dysentery bacillary	1	11	12
German measles	117	47	47
Gonorrhea	258	334	374
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	2	1*
Malaria	1	1	1*
Measles	151	595	296
Meningitis meningococcal	5	7	7
Meningitis Pfeiffer-bacillus	0	1	1
Meningitis pneumococcal	1	0	0
Meningitis staphylococcal	0	0	0
Meningitis streptococcal	0	0	0
Meningitis, undetermined	6	6	4
Mumps	275	428	271
Poliomyelitis	725	68	68
Salmonellosis	74	12	22
Scarlet fever	66	74	157
Syphilis	153	166	310
Tuberculosis pulmonary	236	275	233
Tuberculosis other forms	8	14	15
Typhoid fever	3	6	5
Undulant fever	2	2	5
Whooping cough	479	209	475

*Five-year median

COMMENT

Diseases above the seven-year median were chicken pox, diphtheria, dog bite, German measles, poliomyelitis and salmonellosis.

Diseases below the seven-year median were bacillary dysentery, malaria, measles, scarlet fever, typhoid fever and undulant fever.

Poliomyelitis reached the highest level ever reported for the month, partly owing to the early seasonal rise in the disease. The proportion of nonparalytic cases is higher than that in any previous epidemic year.

Dog bite reached the highest level recorded for August (1284 cases) but was less than in May and June of this year (1472 and 1644).

Diphtheria was at the highest level for August since 1934.

For the third consecutive month, only 1 case of bacillary dysentery was reported.

Scarlet fever dropped to the lowest level ever recorded for the month of August.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Berkley, 2, Boston, 13, Charlton, 2, Gloucester, 2, Milford, 2, Revere, 2, Somerville, 1, Wakefield, 1, Wellesley, 1, total, 26.
Dysentery, bacillary, was reported from Lowell, 1, total, 1.
Encephalitis, infectious, was reported from Salem, 1, total, 1.

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TREATMENT OF INTUSSUSCEPTION CAUSED BY INVAGINATED MECKEL'S DIVERTICULUM

Report of a Case, with a Review of Experience in a Community Hospital

RAYMOND W. GADBOIS, M.D.,* MICHAEL A. DEAN, M.D.,† AND WILLIAM E. JOHNSON, M.D.‡

WORCESTER, MASSACHUSETTS

SINCE we believe that the experience of a small community hospital is of importance in evaluating surgical statistics, it is hoped that the following report will be of interest, particularly in comparison with reports from larger, more specialized hospitals.

Meckel's diverticulum, first recorded by Lavator, described in 1700 by Littre, labeled a diverticulum by Ruysh and Merv, was further reported by Morgagni and finally recognized as a cause of abdominal complaints by John Frederick Meckel.¹

Embryologically, Meckel's diverticulum results from a failure of the intestine to lose its connection with the yolk sac. Developmentally, failure to lose this connection may lead to the diverticulum or persistent omphalomesenteric duct, or any combination of conditions between the two. Statistically, it occurs in approximately 2 per cent of the general population and somewhat more commonly in the male.

Meckel's diverticulum is of importance because it may become inflamed, hemorrhage, adhere to mesentery or bowel, form a nidus of internal hernias, form the focal point of a volvulus or act as a foreign body causing intussusception. For clarity the complications may be divided into primary, including acute inflammation, peptic ulcer, fecal fistula, tumor formation and chronic inflammation, and secondary, comprising intestinal obstruction due to acute inflammatory adhesions, bands and internal hernias, volvulus or intussusception.

Acute inflammatory changes in Meckel's diverticulum may closely simulate the signs, symptoms^{2, 3} and course of acute appendicitis. The natural history of the individual case may vary somewhat depending on the patency and diameter of the stoma, but it may undergo secondary gangrene and necrosis and result in peritonitis by rupture, much in the same manner as an acute appendicitis. Likewise, acute Meckel's diverticulitis has similar serious complications, such as local abscesses with inflam-

matory adhesions and possible intestinal obstruction.

Heterotopic tissue⁴ in the diverticulum occurs more commonly in association with ileal mucosa than ileal mucosa appears alone. Peptic ulceration in close proximity to heterotopic gastric tissue is a well known complication. More often it manifests itself as gross painless melena, but occasionally it erodes through the serosa and gross hemorrhage into the peritoneal cavity results.

The patent persistent omphalomesenteric duct is often diagnosed by the occurrence of a mucoid discharge from the umbilicus. When the duct is widely patent throughout its length,⁵ it serves as a fecal fistula and, if active, can lead the patient into the physiochemical imbalances of an overactive ileostomy.

Tumors as well as tuberculosis can occur in Meckel's diverticulum.

The most important secondary complication of Meckel's diverticulum is intestinal obstruction, manifested in one of the four following ways:

Acute inflammatory adhesions can give rise to an early acute mechanical obstruction. As in any other acute intra-abdominal process, the natural process of containment plasters mesentery, loops of bowel and omentum over and near the site of inflammation. An acute inflammatory mechanical obstruction can be a natural sequela of this process.

Meckel's diverticulum can directly or indirectly cause internal hernias, either as a persistent band from bowel to umbilicus² or by attachment of the free tip to any portion of the visceral or parietal peritoneum, thus forming bands through which bowel might prolapse and be unable to reduce itself. The herniated bowel may vary from a small portion of a loop to a whole segment of bowel, most often, of course, the small bowel. If untreated, the condition may quickly pass through all the stages of irreducible exter-

*Visiting surgeon, St. Vincent Hospital

†Resident in surgery, St. Vincent Hospital

‡Assistant resident in surgery, St. Vincent Hospital

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A meeting of the Middlesex South District Medical Society will be held at the Mount Auburn Hospital, Cambridge, on Wednesday, October 19

PROGRAM

11 30 a m Business meeting

12 00 noon

Discussion of Rheumatoid Arthritis

"Diagnosis and General Management of Rheumatoid Arthritis" Dr Charles Short

"The Adrenal Cortex and Rheumatoid Arthritis" Dr Theodore B Bayles

"The Orthopedic Management of Rheumatoid Arthritis" Dr Robert Joplin

The above presentations will include discussion of differential diagnosis, measures that the general practitioner can apply in the treatment of this disease, the metabolic effects of hormones and the conservative, as well as the surgical measures, in the prevention and correction of articular deformities

A colored moving picture will be shown of the first patient with rheumatic arthritis treated by Cortisone. The running time of this documentary film will be about ten minutes

1 00 p m Luncheon

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, October 18, 12 noon. The speaker will be Dr Charles G Hayden, who will discuss Blue Shield and Blue Cross

Physicians are cordially invited to attend

MASSACHUSETTS ASSOCIATION OF MEDICAL TECHNOLOGISTS, INC

The semi-annual meeting of the Massachusetts Association of Medical Technologists, Inc., will be held at the Berkshire Museum, South Street, Pittsfield, on October 22 from 9 a m to 5 p m

PROGRAM

Medical Application of Radioactive Isotopes Arthur A Hagelstein, M D

Laboratory Diagnoses of Parasitic Diseases of the Intestines in Temperate Climates William Kaufman, M D

Counsellor's Report of the American Society of Clinical Pathologists Donald A Nickerson, M D

Bacteriology in the Small Laboratory David Skinner, M D

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

The American Society for the Study of Arteriosclerosis will hold its annual meeting at the Hotel Knickerbocker, Chicago, on November 6 and 7

SALMON MEMORIAL LECTURES

Dr Stanley Cobb, of Boston, will deliver the Salmon Memorial Lectures at the New York Academy of Medicine on November 8, 9, and 10. The general topic of the lectures will be "Emotions and Clinical Medicine"

LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for 1950 grants-in-aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to January 1, 1950. Support is available for physiologic, biochemical and pathological research that bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about \$550,000 will be awarded for these grants

Applications for postgraduate fellowships for training in research in 1950-51 will also be received by the Fund up to January 1, 1950. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M D or Ph D), or the equivalent, is

required. The annual stipend varies, as a rule being between \$3000 and \$4000, with larger amounts in special cases. At least 12 postgraduate fellowships will be available

New grants and fellowships will become available on July 1, 1950

A number of pre-doctoral fellowships for basic training in research will also be awarded. Details are available on request.

Further information and application blanks may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd Street, New York 29, New York

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3-MAY 19 Massachusetts Department of Mental Health Postgraduate Seminar in Neurology and Psychiatry Page 286, issue of August 18

OCTOBER 10-21 New York Academy of Medicine Page 510 issue of September 29

OCTOBER 11-15 American Society of Clinical Pathologists. Drake Hotel Chicago

OCTOBER 14 Tuberculosis Rehabilitation Society Page 434 issue of September 15

OCTOBER 18 South End Medical Club Notice above

OCTOBER 19 Massachusetts Chapter, American Academy of General Practice Page 550 issue of October 6

OCTOBER 19 Middlesex South District Medical Society Notice above

OCTOBER 22 Massachusetts Association of Medical Technologists Inc. Notice above

OCTOBER 24 Conference of Professors of Preventive Medicine Page 550 issue of October 6

OCTOBER 24-26 National Gastroenterological Association Page 251 issue of August 11

OCTOBER 24-28 American Public Health Association Page 251 issue of August 11

OCTOBER 25 Hampden District Medical Society Page 593

OCTOBER 28 Massachusetts Psychiatric Society Page 434 issue of September 15

NOVEMBER 2 New England Obstetrical and Gynecological Society Hotel Somerset Boston

NOVEMBER 2-5 Pan American Congress of Pediatrics Page 251 issue of August 11

NOVEMBER 3-5 American Association of Blood Banks Page xi issue of June 16

NOVEMBER 6 AND 7 American Society for the Study of Arteriosclerosis Notice above

NOVEMBER 7-9 National Society for Crippled Children and Adults Page 184 issue of July 28

NOVEMBER 7-12 International College of Surgeons Page 251 issue of August 11

NOVEMBER 8 10 Salmon Memorial Lectures Notice above

NOVEMBER 10 Human Streptococcosis Dr Louis Weinstein Pen-tucket Association of Physicians. 8 30 p m Haverhill

NOVEMBER 14-17 American Academy of Pediatrics Page 251 issue of August 11

NOVEMBER 16 Massachusetts State Society of Examining Physicians Page 324 issue of August 25

NOVEMBER 23 Pediatric Seminar for Physicians and General Practitioners Page 550 issue of October 6

DECEMBER 28 AND 29 American Association for the Advancement of Science Page 350 issue of September 1

FEBRUARY 20-23 American Academy of General Practice Page 252 issue of August 11

MAY 3 Norfolk District Medical Society Anniversary Dinner

MAY 16-18 Massachusetts Medical Society Annual Meeting Hotel Statler, Boston

JULY 17 22. International Congress for Scientific Research Page xvii issue of September 1

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 20

FRIDAY OCTOBER 21

*9-00 a m -12 00 m Combined Medical and Surgical Staff Rounds Peter Bent Brigham Hospital

*12-00 m X-Ray Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge

*1 30 p m Tumor Clinic. Out-Patient Department Mount Auburn Hospital, Cambridge

MONDAY, OCTOBER 24

*11 30 a m -12 15 p m Chest X-Ray Conference. South End Health Unit 57 East Concord Street Boston Dr Cleveland Floyd in charge

*12 15-1 15 p m Clinicopathological Conference Main Amphitheater Peter Bent Brigham Hospital

TUESDAY OCTOBER 25

*12 15-1 15 p m Clinicoradiological Conference Peter Bent Brigham Hospital

*1 30-2 30 p m Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital

8 15 p m Hampden District Medical Society Classical High School Springfield

*Open to the medical profession

For our purpose, cases can roughly be divided into three groups occurring in infancy, childhood and adult life. Intussusception is relatively common in the first few years of life, and the greatest proportion of cases occur in the first two years of life. Etiologically no satisfactory explanation for the vast majority of cases can be found. Estimates vary, but it is fair to state that approximately 90 to 95 per cent⁶ of intussusceptions in infancy are found to have no mechanical cause. A few are due to Meckel's diverticulum, intestinal polyp, lymphomas and ileal duplications. In older children the greater number of intussusceptions and in adults almost all have mechanical causes.

Intussusception is a mechanical obstruction and its complications are first partial or complete obstruction with the attending pathologic sequelae. Some intussusceptions produce a maximum of symptoms, progress a short distance and are reducible. Some offer a minimum of symptoms progressing rapidly. Cases are reported with spontaneous expulsion of the intussusception rectally. Between these extremes occur the cases that become incarcerated. Owing to compression of blood vessels venous obstruction, extravasation, anoxemia and infarction of bowel occur. Intra-abdominal rupture with resultant peritonitis may follow. Toxemia occurs fairly soon and if the condition is neglected and allowed to progress, death usually ensues. An analogy can be drawn between an untreated intussusception and an untreated strangulated hernia. The complications and results are similar.

Treatment is, of course, recognition and reduction. Lately, there is a renewed interest in non-operative reduction but the vast majority of surgeons prefer operative intervention so that total pathologic damage can be fully evaluated and the necessary corrective measures immediately applied.

CASE REPORT

An 8-year-old boy was admitted to St. Vincent Hospital on October 5, 1948, with a chief complaint of vomiting. He had been well until 4 days prior to admission, when, after eating breakfast, he complained of "pains in the stomach." This did not keep him away from school but he returned home soon and vomited food residue. During the period before admission he had anorexia and vomited 2 or 3 times a day with short bouts of intermittent abdominal pain. During the 4 days his bowels had been regular except for 4 loose bowel movements with no pain and no blood. On the day prior to admission he vomited twice, once in the morning and again at 11 p.m. The abdominal pain had become no worse. He denied chills, fever, cough and muscle aches. At no time did he have any rash, hematuria or dysuria. On admission the patient appeared listless. The skin was dry, warm and pallid. He had no adenopathy. The lungs were clear, and the only positive physical finding was deep tenderness in the left hypochondrium. There was no palpable mass, no spasm and no costovertebral-angle tenderness. Peristalsis was low pitched and sluggish.

The temperature was 99.4°F, the pulse 98 and the respiration 20.

Examination of the blood disclosed a red-cell count of 5,180,000 with a hemoglobin of 100 per cent, and a white-cell count of 15,500 with 78 per cent neutrophils.

The patient was admitted to the pediatric service with a diagnosis of gastroenteritis. Fluids were forced by mouth and overnight he gradually became somewhat distended and had repeated cramping abdominal pain, most severe in the umbilical region and left upper quadrant. At the time of surgical consultation 18 hours after admission the temperature was 99.4°F, the pulse 104 and the respirations 20. He had not been nauseated and had not vomited during the interval since admission. On physical examination he was alert and co-operative and in moderate discomfort. The abdomen appeared slightly distended and was tympanitic throughout. Tenderness was present throughout the abdomen and maximal in the left upper quadrant. Both rectus muscles were spastic, and the spasm increased with paroxysms of pain. Peristalsis was sluggish and barely audible during intervals between pain and moderately high-pitched and tinkling during the pain. Rectal examination was negative, and no abdominal masses were palpated. A



FIGURE 1 Plain Film of the Abdomen

The localization of the distention to the small bowel suggests mechanical obstruction although it is possible for an adynamic ileus to produce this picture.

plain film of the abdomen revealed marked gaseous distention of the small bowel, with one loop extending well into the pelvis (Fig. 1). An x-ray diagnosis of mechanical obstruction was made.

The surgical service suggested decompression and parenteral administration of fluids, believing that the patient had secondary obstruction on a basis of acute appendicitis, or Meckel's diverticulitis.

After treatment according to the method of Ochsner the patient appeared fairly well and was free of pain but passed no flatus or feces. Peristalsis disappeared. He received penicillin, streptomycin and parenteral injection of fluids. A Cantor tube was passed, and his progress followed by x-ray films. On the morning of the 5th hospital day a firm mass was found in the right lower quadrant and demonstrated by x-ray examination (Fig. 2).

The mass was regarded as representing a localized appendiceal abscess. Throughout the 6th hospital day the pa-

nal hernia, except that operative interference is apt to be longer delayed because of the difficulty in establishing the diagnosis

Acting as the hub on a wheel, the diverticulum may cause volvulus of the small intestine

gressive intussusception requiring reduction or resection in the individual case. The type of intussusception may be ileocolic, ileoileocolic or ileoileal in order of decreasing frequency. When reduction is impossible and more radical measures

TABLE 1 Cases of Meckel's Diverticulum Seen at St Vincent Hospital from 1930 to December 1, 1948

CASE No	AGE yr	SEX	DESCRIPTIVE NOTE	OPERATION	OUTCOME
1	6	M	Invaginated Meckel's diverticulum with intussusception	Reduction of intussusception excision of diverticulum	Recovery
2	5	M	Acute inflammation with perforation	Excision	Recovery
3	39	F	Acute inflammation with perforation intestinal obstruction with adherent loops of bowel	Excision	Recovery
4	18	F	Large patent diverticulum internal hernia through band	Excision	Recovery
5	22	M	Diverticulum (incidental finding)	Excision	Recovery
6	6½	F	Fibrosed band with internal hernia	Excision	Recovery
7	26	M	Acute gangrenous Meckel's diverticulitis with adherent loops of bowel	Excision lysis of adhesions	Recovery
8	18	M	Diverticulum (incidental finding) (in patient's own mesentery)	Excision	Recovery
9	4½	M	Persistent omphalomesenteric duct	Excision	Recovery
10	11	F	Diverticulum (incidental finding)	None	Recovery
11	21	F	Diverticulum (incidental finding)	None	Recovery
12	74	M	Diverticulum (incidental finding)	Inversion choledochogastrostomy for carcinoma of cystic duct	Death from pulmonary edema after operation
13	17	M	Diverticulum (incidental finding)	Excision	Recovery
14	53	F	Diverticulum (incidental finding)	Excision	Recovery
15	8	M	Irreducible intussusception	Resection with end-to-end anastomosis	Recovery
16	31	F	Fibrosed band	Excision	Recovery

By far the most interesting complication is intussusception. Progressive and retrograde intussusception have been reported. Several years ago a comprehensive review recorded only 25 clearly defined cases of obstructing intussusception due to invaginated Meckel's diverticulum

are required, the attending mortality is of serious proportions.

The results of operation in cases of Meckel's diverticulum and intussusception at St Vincent Hospital are shown in Table 1 and 2.

TABLE 2 Cases of Intussusception Seen at St Vincent Hospital from 1930 to December 1, 1948

CASE No	AGE	SEX	TYPE OF INTUSSUSCEPTION	CAUSE	OPERATION	OUTCOME
1	4 mo	F	Ileocolic	Unknown	Reduction	Recovery
2	7 mo	M	Ileocolic	Unknown	Reduction (performed with difficulty)	Death 8 hr after operation
3	7 mo	M	Ileocolic	Unknown	Reduction (performed with difficulty)	Death 4 days after operation
4	10 mo	F	Ileocolic	Unknown	Reduction	Recovery
5	3 yr	F	Colocolic	Unknown	Reduction manually and with enema	Recovery
6	57 yrs	M	Ileoileal	Unknown multiple perforations irreducible	Resection with ileoileal anastomosis and preliminary ileostomy	Death 4 days after operation
7	11 mo	M	Ileocolic	Unknown	Reduction by enema	Recovery
8	79 yr	F	Ileocolic	Adenocarcinoma of cecum	Primary resection, ileotransverse colostomy	Recovery
9	54 yr	F	Ileocolic	Carcinoid of ileum	Resection and primary anastomosis	Recovery
10	42 yr	F	Ileocolic	Carcinoma of cecum	Reduction ileotransverse colostomy	Recovery
11	8 mo	M	Ileocolic	Unknown	Reduction	Recovery
12	4½ mo	M	Ileocolic	Unknown	Reduction	Recovery
13	46 yr	F	Retrograde ileoileal	Carcinoid of ileum	Resection of ileum	Recovery
14	48 yr	F	Colocolic	Adenocarcinoma of cecum	Resection of cecum and ascending colon	Recovery
15	6 yr	M	Ileocolic	Invaginated Meckel's diverticulum	Reduction resection of Meckel's diverticulum	Recovery
16	8 yr	M	Ileoileal	Invaginated Meckel's diverticulum	Resection end-to-end anastomosis	Recovery

More recently, 29 such cases were listed in a series of 610 intussusceptions.⁶ Pathologically, invaginated Meckel's diverticulum occurs as a polypoid mass that can cause partial obstruction, intermittent self-reducing intussusception or pro-

INTUSSUSCEPTION

Intussusception indicates the passage of one segment of bowel into another. It occurs at all ages, varying in frequency and cause at each age period.

DISCUSSION

One of the factors causing a high mortality in patients with irreducible intussusception is the time lost in either hospitalizing the patient or establishing the diagnosis. Later, in our attempts to arrive at a specific diagnosis and in the extensive use of diagnostic aids (x-ray study and so forth), we may on occasion be guilty of what we are sure is just criticism by our older confreres—namely, unwarranted delay in operative exploration.

In this particular case the patient's symptoms were interpreted as being caused by a perforated appendix with peritonitis. He was treated according to the method of Ochsner. When a mass in the right lower quadrant developed, the diagnosis seemed fully established until the mass was noted to move. His abdomen did not distend because of Cantor-tube drainage. There were no physiochemical imbalances, because of adequate parenteral replacement. Toxemia was minimized by intubation, parenteral administration of fluids and antibiotics. When the abdominal mass moved, intussusception was considered, and a barium enema given to establish the diagnosis. Normal barium enema ruled out an enterocolic intussusception. After barium enema, symptoms increased in severity, cramping abdominal pain developed, the patient grew more restless, and the pulse accelerated. In view of the patient's clinical condition operation was considered necessary. At no time had he passed flatus or feces, and no blood was found on rectal examination to aid in the diagnosis. Although the therapeutic triad of suction, fluids and antibiotics without doubt masked the true abdominal picture, their use probably improved the preoperative condition of the patient.

Intestinal obstruction in a child beyond two years of age can be caused by Meckel's diverticulum and should be considered⁷ in differential diagnosis. A history of severe intermittent abdominal pain, vomiting and melena followed by small amounts of bright-red blood is the most reliable diagnostic aid.⁸ Usually, a palpable abdominal mass can be found, although initially it may be small enough to escape detection. With or without the mass the diagnosis should be considered. Later, x-ray proof of intussusception is not being routinely employed^{6,9} because of time lost during the procedure and the fact that a small percentage of cases will not be diagnosed. If the intussusception is an ileoileal one it may be missed, as was true in the case reported above.

Most surgeons believe that the less done, the better in the original reduction. Unless more radical measures are distinctly indicated, they should be deferred to a later operation. Irreducible intussusception is a trying surgical problem, certain to tax the ingenuity and skill of the surgeon and the recuperative resources of the patient. The appalling

mortality attendant upon the established surgical procedures has made surgeons devise newer approaches. Such a change is reflected in the experience of the Boston Children's Hospital⁶ (Table 3).

TABLE 3 Results of Various Types of Operation for Intussusception.

OPERATION	NO OF CASES	NO OF RECOVERIES
Resection with lateral anastomosis	18	3
Open double enterostomy	23	5
Aseptic Mikulicz's resection	14	11

McLaughlin¹⁰ studied 200 cases in a series collected over a forty-year period (Table 4).

End-to-end-anastomosis has been attended with fairly uniform failure in all reports. Dennis¹¹ has reported 8 successful cases, all performed by himself. Penberthy and Benson⁷ described 2 consecutive failures, 1 patient dying four hours postoperatively in shock, and the other sixteen days post-

TABLE 4 Results of Operation in 200 Cases of Intussusception

OPERATION	NO OF CASES	MORTALITY
Resection and anastomosis	146	67.8
Maunsell's procedure	8	100.0
Lateral anastomosis	15	26.6
Colostomy or Mikulicz's procedure	31	87.0
1937-47		
Resection and anastomosis	48	39.0
Maunsell's procedure	2	100.0
Lateral anastomosis	7	43.0
Colostomy or Mikulicz's procedure	11	73.0

operatively of secondary bowel obstruction. Miller¹² believes that the type of operation depends upon the circumstances. Many will permit resection and anastomosis, but most often one will be fortunate in being able to perform a successful exteriorization. Barnes¹³ recently suggested a neat extraperitoneal resection, in which a primary serosal layer of sutures is placed between the intussusceptum and intussusciens. The intussusciens is sutured to the peritoneal edges just below the anastomosis. When the peritoneum is closed about this site, an opening is made in the intussusciens, and the intussusceptum is drawn out and pegged at the anastomosis with guide sutures. The intussusceptum is removed with cautery, and an internal hemostatic layer of sutures is placed. With the guide sutures as countertraction, a small catheter is threaded back into the small bowel proximal to the anastomosis. This serves as an immediate ileostomy, decompressing the bowel proximal to the anastomosis protecting the suture line. By this means a completely extraperitoneal resection is possible.

patient experienced cramping abdominal pain. The mass moved to the epigastrium and then later was found in the left hypochondrium. The abdomen was soft and nontender, with no tenderness over the mass. The pulse had risen to 132, and a diagnosis of progressive intussusception was made. Barium enema revealed a normal colon and distal ileum. The previously noted mass in the right lower quadrant was absent on x-ray study (Fig. 3).

The patient was returned to the ward for continued observation. During the night he required Demerol for pain. In the morning he was observed during an attack of pain in which he doubled his legs up on his abdomen. However, the abdomen was soft and nontender with the mass again in the right lower quadrant. Operative interference was elected. The preoperative diagnoses were internal hernia, volvulus and omental cyst with ?volvulus.

Dilated loops of small bowel extruded through the abdominal incision. The aforementioned mass was easily

When the specimen was opened, the head of the intussusceptum was found to be an invaginated Meckel's diverticulum (Fig. 4).



FIGURE 3 Roentgenogram of the Abdomen in Which the Soft Tissue Mass Previously Observed in the Right Lower Quadrant Is No Longer Apparent

The small bowel remains distended but slightly less so than on the initial examination. After a barium enema the colon filled easily and normally, and the barium also passed freely into the terminal ileum. The appendix filled in the normal position. No pressure defects could be demonstrated on the bowel, and there was no evidence of disease in the colon.

Postoperatively the patient's convalescence was complicated by peritonitis, which quickly subsided, and he was



FIGURE 2 Roentgenogram Taken with the Tip of the Cantor Tube in the Duodenum

A fairly definite soft-tissue mass is outlined in the right lower quadrant. The small-bowel distention appears less at this time.

found, mobilized out of the right lower quadrant, and proved to be an ileoileal intussusception, the intussusceptum measuring approximately 46 cm. With gentle milking behind the head of the intussusceptum a reduction back to approximately 14 cm from its origin was possible. When greater pressure was exerted, a transverse tear occurred in the serosa. Taxis on the intussusceptum was ineffectual, and immediate resection was considered necessary. The abdominal cavity was packed off. The loop of bowel was brought out on the abdomen and the entire procedure performed extra-abdominally. Viable bowel was selected proximally and distally and divided between clamps with cautery. A primary end-to-end anastomosis with three layers of sutures was performed. The bowel had been sectioned at an angle of about 70° to ensure an adequate stoma, and the little finger could easily pass through the stoma. The site of the anastomosis was determined to be approximately 75 cm from the ileocecal valve.



FIGURE 4 Opened Specimen, Showing How the Meckel Diverticulum Invaginated and Acted as the Head of the Intussusceptum

discharged well on the 13th postoperative day with the wound healed by first intention.

DISCUSSION

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SUMMARY

The experience of a general hospital with both Meckel's diverticulum and intussusception in all age groups is presented

Attention is called to one of 3 unusual cases, which is reported in detail, with successful resection and primary end-to-end anastomosis

Some features of both Meckel's diverticulum and intussusception are reviewed

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THE TREATMENT OF SNAKE-BITE POISONING*

A Report of Two Cases Involving the Copperhead

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IT IS indeed a rare occasion when a physician in New England is called upon to treat a bona fide case of snake-bite poisoning although the same statement certainly cannot be made of the false alarm

The following experience is related not primarily to suggest an ideal routine for handling poisonous snake bites, but rather to call attention to the fact that such cases can occur in New England and to suggest that there should be in the mind of every physician a rational plan for emergency and definitive therapy The opinions of others with extensive experience in this problem are at the same time reviewed

The poisonous reptile in these cases was the copperhead (*Agkistrodon mokasen*). It is a member of the pit-viper family, represented in the United States also by the rattler and the cotton-mouth moccasin, which is not native to New England The only other poisonous North American snake, the coral snake, is also found only in warm climates Although this discussion is limited essentially to matters concerning the copperhead, the bites of these three members of the pit-viper family have much in common In a review of the literature no clinical report of a copperhead bite could be found

CASE REPORTS

CASE 1 R M, a 49-year-old farmer, was seen on June 7, 1947, about 15 minutes after receiving the bite of a snake, which he thought was probably a copperhead He had been picking up kindling wood in a woodland lumber shed when the bite occurred (it was a cold rainy day in the spring, and

the snake had hidden in the dry leaves under the wood pile) He had immediately applied a tourniquet to his forearm tightly enough to prevent the venous flow, but not to occlude the radial or ulnar arterial flow On the dorsal surface of the middle phalanx of the middle finger were two puncture holes about 1 cm apart, and 2.5 cm distal to this were three or four smaller scratch marks A small amount of bloody serum was oozing from the puncture holes The patient had been squeezing his finger in this area hoping to express some of the venom, but apparently only bloody fluid was obtained. At the time he appeared in my office, only 15 minutes after the bite, edema had already developed in the involved finger extending proximally to its base and 2.5 cm or so over the back of the hand

Two criss-cross incisions, about 1 cm deep, were immediately made directly over the puncture holes, and bright red blood was obtained spontaneously and by expression Two similar incisions were made over the edematous area proximally, and blood tinged serum was obtained At this point, some 30 minutes after the occurrence of the bite, the tourniquet was removed because of severe pain in the hand, which was attributed to the tourniquet but in all probability was due rather to the irritating effect of the venom The tourniquet was reapplied a few minutes later, and after about another ½ hour was discarded

Since there was no actual proof of the identity of the snake, a search of the shed was made, and after several pieces of kindling had been removed, a copper-colored snake was uncovered It appeared very lethargic but when teased with a stick struck viciously at it Upon verification of the snake's identity the farmer was removed to the New Britain General Hospital for further treatment While searching for the snake he experienced chilliness and complained of general malaise On admission to the hospital, about 3 hours after the bite, he was given intramuscularly 15 cc of Lyovac, a polyvalent antivenin prepared from horse serum for the treatment of any of the three North American pit-viper bites Three thousand units of tetanus antitoxin was also given prophylactically, penicillin in doses of 30,000 units every 3 hours was started, in view of the extensive edema and the well known possibility of infection in such cases

Two further criss-cross incisions were made proximally on the wrist. No suction was applied to the puncture wounds, which were oozing clear serum In retrospect, thorough suction should have been attempted over the puncture wounds as well as the other incisions, and in this way perhaps some

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of the subsequent edema could have been avoided. No potassium permanganate crystals or other medication was applied locally, nor was antivenin injected locally.

On admission, the vital signs were normal, and the remainder of the physical examination was essentially negative. During the night, however, the temperature rose to 100°F by mouth. The patient felt and looked quite ill. There was considerable nausea associated with about six episodes of vomiting. His main complaint was a rather severe pain in his hand and arm lasting about 48 hours. On the following morning the edema had spread to the elbow, and by evening to the axilla. In view of this, an additional 15 cc of antivenin was given and again repeated a few hours later. On the next day, 48 hours after the bite, the edema had spread to involve the shoulder and was extending laterally down the thorax. This area of edema over the thorax was about 20 cm in diameter and 5.1 to 7.6 cm in depth. The central part was characterized by a yellow and black discoloration, and the peripheral "advancing" border was warm and erythematous, fading on pressure. The left arm measured

On the morning of admission the hematocrit was 51 per cent. The nonprotein nitrogen was 35 mg per 100 cc, and the sedimentation rate 2 mm in 1 hour. The white-cell count was 12,300, with 81 per cent segmented and 2 per cent non-segmented forms, 15 per cent lymphocytes, and 2 per cent monocytes. The hemoglobin was 103 per cent. On the 2nd day the bleeding time was 30 seconds, and the clotting time 3 minutes. On the third day the white-cell count was 6300, with 89 per cent segmented and 3 per cent non-segmented forms, 7 per cent lymphocytes and 1 per cent monocytes, and the hemoglobin 89 per cent. The blood serologic findings were negative. The urine on admission gave negative tests for albumin and sugar and had a specific gravity of 1.024. The sediment contained 0 to 2 pus cells and 10 to 12 red blood cells per high-power field. At the time of discharge there were still 1 to 3 red blood cells and 1 or 2 white blood cells per high-power field in the spun specimen.

CASE 2 J. L., a 19-year-old high-school student, was admitted to the emergency room of the New Britain General Hospital at 12:30 a.m. on May 2, 1949. He stated that about ½ hour before admission he had been fishing in a local reservoir, an area known to be infested with copperhead snakes. While walking about the shore of the reservoir, he felt a sudden needle-like jab in his right ankle. In the darkness it was impossible to identify the snake that had bitten him, but in view of the presence of copperheads in this area and in the absence of a rattle it was assumed that the snake was a copperhead. The patient did nothing in the way of first aid for the bite, reporting directly into the hospital. Being alone, he rode in on his bicycle, the entire trip taking about 20 minutes. While riding his bicycle, he noted pain and stiffness in the ankle and a slight chill sensation, but no shaking chills or prostration.

On admission he appeared anxious and in some discomfort owing to the bite. Examination revealed a well developed, well nourished boy. There were two pin-point puncture wounds, approximately 1 cm. apart, situated on the inner surface of the right ankle approximately 1 cm. behind the internal malleolus. There was a bloody, serous discharge from both wounds. There was also at this time, approximately 20 minutes after the bite, swelling, redness and tenderness of the entire ankle extending upward to about 7.6 cm. above the malleolus. Palpation in the popliteal space was slightly tender, and there was tenderness extending up the inner aspect of the thigh to the groin, where the lymph nodes were slightly enlarged and also tender.

The temperature was 98.6°F, the pulse 78, and the respirations 20. The blood pressure was 118/60.

Examination of the blood showed a hemoglobin of 92 per cent (14.4 gm) and a white-cell count of 11,300, with 68 per cent segmented and 11 per cent nonsegmented forms and 21 per cent lymphocytes. The urine had a specific gravity of 1.024, with negative tests for albumin and sugar, and the sediment contained 0 to 1 pus cells and 0 to 1 red cells per high-power field. The prothrombin time on the morning of admission was 100 per cent of normal (16 seconds), and the sedimentation rate 4 mm. per hour. The blood serologic findings were negative. The nonprotein nitrogen was 42 mg per 100 cc.

On admission to the emergency room, a tourniquet tight enough to prevent venous return was placed about the patient's thigh, and two linear incisions about 2 cm. in length were made over both puncture holes. These incisions were then irrigated with saline solution and were suctioned thoroughly for about 15 to 20 minutes hourly for the next 10 hours. The tourniquet, which at first had been applied at the thigh, was reapplied at the ankle just above the line of edema. After an intracutaneous test for horse serum sensitivity, to which the patient was negative, 15 cc. of polyvalent snake serum was injected intramuscularly. At the same time he was given 3000 units of tetanus antitoxin, 1 cc. of penicillin in oil (300,000 units) was given twice daily during the period of hospitalization. Pyribenzamine, 50 mg., was given four times daily. On admission the right ankle was 50.5 cm., the left ankle 27.9 cm., the right calf 36.8 cm., and the left calf 36.2 cm. in circumference on the following day respective measurements were 28.6, 27.9, 36.8 and 36.8 cm. On the leg itself, which was kept flat, there appeared a yellow-blue, very tender discoloration along the lymphatic circulation of the inner aspect of the calf and inner aspect of



FIGURE 1 Film Taken on the Fourth Day in Case 1, Showing Edema of the Left Arm and Thorax

5.1 cm. larger in circumference than the right at the mid-forearm, 6.3 cm. at the elbow and 7.6 cm. at the mid-arm (Fig. 1). On the next day, the edema of the arm had begun to subside, and the arm was only 1 cm. larger at the mid-forearm, 3.8 cm. at the elbow and 3.2 cm. at the mid-arm. Associated with the edema was an exquisite tenderness and swelling of the epitrochlear nodes noted on the evening of admission, followed by tenderness in the axillary nodes, which were still tender even at the time of discharge on the 5th hospital day. About 96 hours after the bite, the edema of the thorax had descended to the crest of the ilium, gradually disappearing on the next day. No gangrene or slough appeared at any time, although two 1.5-cm. blisters filled with amber-colored fluid developed on the bitten finger. Edema could be detected in the involved forearm for about 3 weeks, and in the afflicted finger for about 5 weeks after the bite.

The arm was maintained on two pillows, and the patient lay in a recumbent position as tolerated. He was up and about on the 4th hospital day.

The temperature remained elevated at 100°F by mouth for 3 days, becoming normal on the 4th; the vital signs otherwise remained normal throughout. The blood pressure was 130/80, the pulse 70, and the respirations 20.

Supportive treatment was minimal, consisting of hot wet magnesium sulfate packs to the hand, Benadryl three times a day for 2 days, and a regimen of forced fluids.

On the 8th day after discharge, a mild serum sickness, characterized by urticaria and nausea, appeared and was treated satisfactorily with antihistamine drugs.

the thigh. This discoloration gradually became darker but less tender in the next 48 hours.

In view of the benign course that the patient was running, he was discharged from the hospital on the 3rd hospital day approximately 60 hours after admission.

At home he was allowed to be up and about, and under this treatment the residual swelling in the right ankle disappeared in about 1 week. The discoloration along the lymphatics lasted approximately 2 weeks. When last seen in the office, approximately 3 weeks after the bite, the patient felt entirely well, and the leg appeared normal. There was a moderate urticarial serum-sickness reaction 1 week after injection of the serum.

DISCUSSION

In New England only two types of poisonous snakes are found, the copperhead and the rattlesnake, both members of the pit-viper family.¹ The term "pit" refers to a small hole on either side of the skull just in front of the eyes. The copperhead introduces its venom into its victim by way of two "hypodermic" fangs situated on the upper jaw. These lie folded flat up against the roof of the mouth when the mouth is closed, but project directly forward on a hinge-like arrangement when the mouth is open in the act of striking. These fangs are approximately 1 cm long and are partially covered by the mucous membrane of the mouth, which peels off the teeth when the mouth is stretched open. In addition to these two fangs, there are rows of teeth on the upper and lower jaws. Although an accurate bite pattern could not be made out in the cases reported above, the two fang marks could be seen very plainly. The marks made by the lower teeth in Case 1 were also noted, but these could not be counted individually. For practical purposes, if the fang marks are absent, one can guess that either the snake was not a member of the pit-viper family — and hence, in New England, not a poisonous snake — or, less likely, the bite was superficial and no venom was injected into the victim. This point may be of major diagnostic significance when the true identity of the snake is unknown.²

Once the fact has been established that one is actually dealing with the bite of a venomous snake, the treatment falls into four general phases — namely, first-aid therapy, the use of antivenin, the prophylaxis of infection and the application of general supportive measures. It seems that prompt first-aid management is of considerable importance in the prognosis of these cases. Ideally, the limb is placed at rest in a dependent position, a tourniquet lightly applied proximal to the bite, and immediate incision and suction of the incision performed as soon after the bite as possible.^{3, 4} This method has been accepted for years, one of the first reports appearing in the literature in 1927.⁵ Multiple incisions and suction should be made in a staggered fashion, circling the limb at higher levels as the edema advances. It is the opinion of some authorities^{3, 5} that most patients are undertreated, and few, if any, overtreated. It is suggested that in a severe bite, 50 to 100 small incisions be made

and suction continued for twenty minutes every two hours for thirty-six hours.³ The tourniquet is applied lightly, since absorption of the venom is by way of the lymphatic rather than, primarily, the venous system. The copperhead bite however, usually does not appear to be fatal in adults, and such vigorous treatment may probably be deferred.

Other local therapy such as the use of potassium permanganate crystals no longer seems indicated.

A polyvalent antivenin derived from horse serum and said to be effective for all North American poisonous snakes, except the coral snake, should be given immediately in the usual 15-cc dose. It is suggested by some workers that five, ten or even fifteen doses be used in severe bites and that a single 15-cc dose is practically of no value. (Strangely enough, however, it is believed by others that the life-saving property of this antivenin is due to the gas-gangrene antitoxin that is produced in the horse inoculated with the venom of the snake presumably containing the gas bacillus, rather than to the antivenin factor itself.) In children, since the body weight is less and the concentration of venom per kilogram thus greater, a larger dose of antivenin is necessary than in the adult. It goes without saying that since antivenin is a product of horse serum, its administration should be preceded by the usual test for sensitivity. Antivenin may be administered subcutaneously, intramuscularly or, if symptoms are severe, intravenously. It is preserved in a powdered state and must first be dissolved in distilled water. If the patient is seen within the first two hours, half the initial dose — that is, 7.5 cc — should be injected locally. The amount of antivenin in one 15-cc ampoule is said to neutralize the amount of venom necessary to destroy 50 pounds (22.6 kg) of body weight.⁶ On the basis of this ratio it seems that three or four ampoules contain sufficient antivenin for the ordinary case. The patient in Case 1 received three ampoules, and the patient in Case 2 only 1 ampoule. After bites from rattlesnakes and larger moccasins, in general, a larger dose is indicated.

The use of antibiotics — as in this case, penicillin — is indicated in the prophylaxis of secondary infection. Tetanus antitoxin is also indicated in view of the frequent occurrence of tetanus following snake bites.⁶ Wet dressings are suggested for ulcerative areas that may develop.

General supportive care consists chiefly in the treatment of shock, if it occurs, with the use of blood or plasma, preferably blood. Since many patients have experienced either vomiting or diarrhea, fluid and electrolyte balance must be adjusted. Hemolytic anemia in severe rattlesnake bites may produce a drop of 2,000,000 in the red-cell count.⁶ In Case 1 the drop in hemoglobin was ascribed to the effect of dehydration and subsequent hydration. No hemoglobinuria or jaundice was noted, although hematuria apparently due to renal irritation did

occur. As noted in the case reports, these patients required a minimum of supportive care.

The most striking evidence of a pit-viper bite is the characteristic edema, usually painful, which develops almost immediately after the bite. This is due to the effect of the injected venom. Copperhead venom is an albuminoid, the exact chemical nature of which is unknown. It is a violent irritant, producing a proteolytic and cytolytic effect on the tissues locally and a hematotoxic or hemolytic effect on the red blood cells systemically. Although this venom is eventually absorbed into the lymphatics, the course of the edema suggests that its circulation and movements through the tissues occur primarily by way of the tissue spaces. This supposition of "drifting" of venom is justified on the basis of observation of these and other reported cases⁴ of pit-viper bites that the edema readily ascends above known levels of communicating lymphatics — that is, into the shoulder girdle and chest wall in cases of snake bites of the hand — instead of converging into the axilla. In view of the obnoxious characteristics of this venom one might certainly hesitate before using mouth suction in removing it from the puncture wounds, particularly in the presence of gingivitis or similar oral lesions. The application of a square of rubber over the bite to protect the mouth has been suggested in emergencies. (Facial bites by the Habu snake of Okinawa in one case recently reported caused edema of the respiratory passages and respiratory embarrassment.)

Although the emergency treatment in Case 1 was inadequate, at least so far as suction was concerned, at no time in retrospect does it appear that the patient's life was in jeopardy. Statistics prepared by the Antivenin Institute of America⁷ indicate that the yearly number of poisonous snake bites in this country may amount to 2000 or 3000, the death rate varying from 10 to 35 per cent. Over a twenty-year period ending in 1945, there were 2385 deaths from poisoning by venomous animals in the United States, and only 9 of these were in Connecticut, where this bite occurred.⁸ These deaths include bites of spiders, centipedes and snakes of all types, and no current list of the number of fatal snake bites or of the number of deaths specifically due to the copperhead exists. In New England over a period of the last five years, there were 6 deaths due to venomous animals, none occurring in the relatively snake-free states of Maine and Vermont. Although little information could be found regarding the mortality due to copperhead bites per se, one

gathers that in adults the mortality should be negligible.

SUMMARY

The clinical course and treatment of 2 cases of poisonous snake bite (copperhead) are reported.

Only two poisonous snakes, the copperhead and the rattlesnake, both members of the pit-viper family, are found in New England, the habitat of the two other poisonous snakes in the United States, the moccasin and the coral snake, being warmer climates.

The typical pit-viper bite reveals a pattern of two prominent fang marks and is associated with immediate pain and extensive edema. If these findings are absent the bite can be considered harmless (in New England, that is).

Treatment consists essentially of the early application of a tourniquet, followed by incision and suction and the administration of three or four ampoules of antivenin. Part of this may be injected locally. The dosage varies with the size of the snake and the severity of the symptoms.

Children must be treated more vigorously than adults since the concentration of venom per kilogram of body weight is greater.

Tetanus and secondary infection should be treated prophylactically.

The prognosis for copperhead bites in adults properly treated should be good.

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BENIGN GASTRIC ULCERS OCCURRING IN THE PRESENCE OF ACHLORHYDRIA*

Report of Two Cases

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OVER a period of years there has been a great deal of controversy in the literature regarding the possibility of benign gastric ulcers in the presence of an achlorhydria. Several carefully prepared reports tend to prove that achlorhydria does not exist in the presence of an active ulcer. Palmer and Nutter¹ reviewed 2200 cases of proved duodenal and gastric ulcers in 1940 and found in no case a persistent and total achylia. Bockus² agreed with this in his textbook stating that "true achlorhydria is not found in patients with active peptic ulcer." Washburn and Rozendaal³ reported a series of 906 cases of pernicious anemia, in none of which an ulcer was found. Kahn⁴ also reviewed 840 cases of pernicious anemia without finding any coexisting ulcers.

There has been opposing evidence presented from time to time, such as the paper by Vanzant et al.⁵ in 1933, in which cases of benign gastric ulcers were found in the presence of achlorhydria. Their tests were, however, performed after Ewald meals only. Bockus and Bank,⁶ in 1927, had already shown the value of checking these tests with histamine analysis. Ruffin and Dick,⁷ in 1939, reported a 54 per cent incidence of achlorhydria in a series of 419 cases of duodenal ulcers and a 67 per cent incidence in 42 cases of benign gastric ulcers. However, they used only a single extraction of gastric juice three quarters of an hour after histamine, and the diagnoses were made by roentgenologic examination alone without surgical or microscopical confirmation.

A summary of the objections raised regarding the reported cases of benign ulcer with achlorhydria is as follows: a single test for free gastric acid is inaccurate, the Ewald or Rehfuess test was run for too short a time, a single histamine analysis was made when the sample of gastric juice was taken too soon after the histamine injection, proof was lacking that the histamine used was pharmacologically active, the Ewald or Rehfuess meal test was not confirmed by a histamine analysis, the gastric analysis was not done at the time the ulcer was known to be active, and the diagnosis of benign ulcer was not absolutely confirmed by microscopical examination. Too frequently patients are seen with gastric ulcers that have been diagnosed clinically, roentgenographically and pathologically

(gross) as a benign ulcer only to discover from microscopical examination that cancer is present.

A recent paper by Ricketts and his associates⁸ pointed out that, by definition, the term "peptic ulcer" implies the presence of both free hydrochloric acid and pepsin. It is proved that peptic activity occurs at an optimum hydrogen ion concentration, which requires acid present to attain this concentration. It is also a more or less accepted belief that "peptic ulcers" are caused by the action of acid and pepsin on a mucosa that has been altered in some manner and is now susceptible to this digestive action.

With all these points in mind we consider the following 2 cases worth reporting since both patients had a persistent achlorhydria—by both Ewald meal and histamine tests with the histamine test carried out to seventy-five minutes on each occasion. Clinically, the histamine used in the tests appeared to be pharmacologically active. Both patients had clinical courses indistinguishable from those of patients with benign gastric ulcers (so-called "peptic ulcers"). Pathologically, on gross and repeated microscopical examination, Dr. William A. Meissner found only benign ulceration. In both cases other causes of ulceration of the stomach such as trauma, gastritis of specific origin, syphilis, tuberculosis, foreign body and local vascular disorders, could be excluded, arteriosclerosis was present generally, but no local changes were found in the vessels in the pathological specimens.

CASE REPORTS§

CASE 1. A 69-year-old retired man entered the Lahey Clinic on October 5, 1948, complaining of epigastric pain for a period of 3 or 4 years occurring 3 or 4 hours after meals and sometimes relieved by food and by sodium bicarbonate. There had been times when this pain required morphine by injection for relief. He had never been free from the pain for more than 2 days at a time during this period. His appetite had been poor for the past 4 or 5 months, and he had noted some difficulty in swallowing meat. He complained of belching and flatulency for a period of years, and for the past few months had vomited about once a week. He had had one black stool about 6 months previously, and he had been taking no medication at the time. He complained of constipation over a period of years for which he had been using daily laxatives. A 17-pound weight loss had occurred during the past year.

A review of the systems, past history and family history were noncontributory.

Physical examination revealed that the patient weighed 86 pounds. He was cachectic and pale. There were beginning cataracts of both eyes. The tongue was smooth and fairly

He had no free gastric analysis (free acid recorded as a histamine analysis) was done after an Ewald meal consisting of plain soda crackers and water.

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moist, and some senile emphysema was present the posture was poor, and there was coldness of the extremities. Dorsalis-pedis pulses were not obtainable, and moderate peripheral arteriosclerosis was present.

The blood pressure was 130/70, and the pulse 80.

Urinalysis was negative. Examination of the blood disclosed a red-cell count of 4,150,000, with a hemoglobin of 14.1 gm (90 per cent), and a white-cell count of 6900, with a normal differential. The blood sedimentation rate was 23 mm per hour, and the blood Hinton reaction was negative. A stool examination revealed no occult or gross blood. The nonprotein nitrogen was 29 mg and the total protein 5.6 gm per 100 cc., with an albumin-globulin ratio of 1.8 to 1. The chloride was 96 milliequiv per liter, the cephalin flocculation ++, and the blood phosphorus 2.7 mg per 100 cc. A gastric analysis done after an Ewald meal on October 6 revealed no free acid with a total acidity of 10 units. Gastric analysis after an Ewald meal on November 16 disclosed no free hydrochloric acid, with a total acidity of 2 units. Gastric analysis carried out on November 16 after histamine revealed no free hydrochloric acid throughout, and no acidity was found. (The test was carried out for 75 minutes.) Proctoscopic and barium-enema examinations were negative.

A roentgenogram of the upper gastrointestinal tract showed a gastric ulcer measuring about 1 cm in diameter projecting from the lesser-curvature side of the stomach at the junction of the cardia and body. There was an hour-glass appearance below this. The rest of the upper gastrointestinal study was negative.

In view of the patient's age, clinical history, roentgenologic findings, achlorhydria and poor relief under medical management, a preoperative diagnosis of cancer of the stomach was made, and he was admitted to the New England Deaconess Hospital on November 15.

During his hospital stay a gastric resection was carried out. At operation an ulcer of the lesser curvature of the stomach at the junction of the upper and middle thirds was found surrounded by multiple adhesions. It was impossible to tell whether this was benign or malignant grossly. The operation consisted of partial gastric resection and an end-to-side retrocolic gastrojejunostomy done by the Hofmeister technique.

Microscopical examination on multiple sections (at least 30) of the specimens revealed no evidence of any malignant degeneration, and a diagnosis of benign ulcer of the stomach was made. (Thirteen lymph nodes were also examined and found to be normal.)

Postoperatively, the course was complicated by upper abdominal pain, vomiting and pain in the chest. The medical consultant thought that the patient also had arteriosclerotic heart disease, chronic pulmonary emphysema, chronic bronchitis and malnutrition. Digitalis was given, and potassium iodide administered intravenously, and under this therapy he rapidly improved. He was discharged from the hospital on December 11 improved, on a bland diet, five small feedings a day, accessory vitamins and proper rest.

He was subsequently seen on January 11, 1949, when he weighed 88½ pounds and still complained of some pain in the epigastrium after meals and some diarrhea. A recent letter from him informs us that he has no pain now and is gaining weight.

CASE 2. A 64-year-old married coppersmith was first seen at the Lahey Clinic on January 28, 1944. He complained of epigastric pain of 1 year's duration occurring about 1 hour after meals and awakening him at 1 or 2 a.m. The pain was relieved by alkali and cream. He also complained of the feeling of a lump in the right upper abdominal quadrant and of chronic constipation over a period of years requiring frequent cathartics. The epigastric pain was periodic, leaving him for weeks or more with complete freedom. A roentgenogram of the upper gastrointestinal tract elsewhere had disclosed an ulcer.

A review of the system, and the past and family histories were noncontributory.

On physical examination the patient weighed 138 pounds. Examination of the abdomen revealed tenderness with some muscle guarding on the right side. The right lobe of the prostate was slightly enlarged. The remainder of the physical examination was within normal limits.

The blood pressure was 110/60, and the pulse, respiration and temperature were normal.

Examination of the blood at this time revealed a red-cell count of 4,820,000, with a hemoglobin of 15.1 gm (97 per cent), and a white-cell count of 5500. The blood Hinton reaction was negative. Gastric analysis revealed 60 per cent food content, no free hydrochloric acid, a total acid of 8 units and no occult blood. Examination of the urine showed slight albuminuria, no sugar, a specific gravity of 1.030, an acid reaction and no formed elements.

Roentgenograms of the large intestine and gall bladder were completely normal. A roentgenogram of the upper gastrointestinal tract revealed a normal esophagus but high on the lesser curvature of the stomach was a 1.5-cm out-pocketing, with some thickening and distortion of the rugal pattern of the fundus. This was interpreted clinically as a gastric ulcer, probably malignant because of achlorhydria.

In view of this the patient was admitted to the New England Baptist Hospital on February 7. An exploratory laparotomy was performed, and he was found to have a benign gastric ulcer. Biopsy specimens of the ulcer and the lymph nodes around the omentum were normal microscopically. Postoperatively atelectasis of the left lower lobe of the lung developed, with associated pneumonitis. He recovered from this and was discharged from the hospital on February 25. During his hospital stay he had been managed on a strict ulcer type of dietary management, rest, antacids and antispasmodics.

After this hospitalization he was seen periodically. In April a gastric analysis after an Ewald meal still revealed no free hydrochloric acid, with a total acid of 11 units. Examinations of the blood and urine were negative. Roentgenograms of the upper gastrointestinal tract at that time showed that the gastric ulcer measured only 1 cm in its greatest extent.

The patient was also seen in July, when a free hydrochloric acid of 2 units was found, with a total acid of 8 units on gastric analysis. The blood was normal and a repeat gastrointestinal series at this time revealed that the ulcer had completely healed.

In January, 1945, a gastric analysis demonstrated no free hydrochloric acid and a total acid of 8 units. The blood was normal, and a roentgenogram of the upper gastrointestinal tract revealed no abnormalities.

He was seen again in September, 1947, complaining of a recurrence of epigastric distress, and again physical examination was negative. The blood pressure was 120/80. At this time gastric analysis showed no free hydrochloric acid and a total acid of 8 units. The blood was normal, and examination of the urine negative. A roentgenogram of the upper gastrointestinal tract revealed prepyloric and antral spasm but was otherwise normal.

The patient returned to the clinic in October when a histamine gastric analysis was carried out. A specimen was taken 15 minutes, 30 minutes, 45 minutes, 1 hour and 1½ hours after histamine. The test revealed no free hydrochloric acid with a total acid of 6, 8, 4, 10 and 12 units, respectively. Roentgenograms of the stomach disclosed narrowing of the antrum of the stomach but were otherwise normal. Examination of the blood at this time was normal.

The patient was again seen in December, when a gastric analysis demonstrated no free hydrochloric acid and a total acid of 15 units. The blood was normal and a roentgenogram of the upper gastrointestinal tract revealed no abnormalities.

In January, 1948, gastric analysis demonstrated no free hydrochloric acid and a total acid of 5 units. The blood was normal. In March the blood was still normal. Roentgenograms of the upper gastrointestinal tract revealed recurrence of an ulcer on the lesser curvature of the stomach, with a possible filling defect at the base of the ulcer. The patient was therefore readmitted to the New England Baptist Hospital on April 18 and a high subtotal gastric resection was carried out. In view of the fact that past history included achlorhydria, the specimen was examined with extreme care microscopically, but no evidence of cancer was found and therefore the presence of a benign gastric ulcer with a chronic gastritis was confirmed. Lymph nodes taken from the region at operation were also negative for malignant change. He was discharged from the hospital on May 4, after an uneventful postoperative course, although a further diagnosis of Paget's disease of the pelvis was made at this time.

The patient was readmitted to the hospital on May 18 because of vomiting and lack of appetite. Levine-tube drain-

age of the stomach was instituted for 24 hours, after which he had again responded well and was discharged on May 27.

In October he returned for examination. He had done well except for fainting spells, which the neurosurgical consultant thought were probably on the basis of cerebrovascular disease, but he had had no further gastrointestinal complaints. The blood was normal and a gastric analysis revealed no free hydrochloric acid and a total acid of 20 units. A barium meal demonstrated a normally functioning, subtotally resected stomach and gastroenterostomy.

DISCUSSION

If we take shelter in the definition of peptic ulcer that automatically excludes any benign ulcer with an accompanying achlorhydria, further discussion is unnecessary. However, if we admit the possibility that peptic ulcers may occur under these circumstances it adds one more item to the general problem of peptic ulcer. We consider the 2 cases reported to be clinically indistinguishable from benign "peptic ulcers," and yet we have fairly well proved the existence of an achlorhydria in both. We have also excluded as far as possible any specific etiology for the gastric ulcers. It is interesting to note that in both cases parietal and chief cells were found in the gastric mucosa microscopically.

SUMMARY

Reports concerning the pros and cons of ulcer and achlorhydria are briefly enumerated.

Two cases of benign active gastric ulcers in the presence of persistent achlorhydria are reported.

Pathological confirmation was obtained through the kindness of Dr. William A. Meissner, of the Department of Pathology, New England Deaconess Hospital.

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THE EFFECTS OF A SINGLE DOSE OF 2000 UNITS OF PROTAMINE ZINC INSULIN TAKEN BY A DIABETIC PATIENT WITH SUICIDAL INTENT*

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THE effects of exceedingly large doses of protamine zinc insulin are known chiefly from patients who have taken excessive amounts by error.¹ The literature, however, also lists 2 cases in which huge quantities were taken with suicidal intent, 490 units in the first case and "one bottle" in the other.² These observations indicate that overdosage with protamine zinc insulin is characterized by a definite sequence of symptoms.

Since the effect of protamine zinc insulin on the blood sugar level develops much more slowly than that of unmodified insulin, there is a considerable initial period during which the compensatory mechanisms (chiefly increased liberation of epinephrine) are able to maintain a more or less adequate blood sugar level by mobilizing the available glycogen in the liver.¹⁻³ However, once the glycogen stores are exhausted, the production of epinephrine is no longer of any avail, and, with the further uptake of insulin from the protamine zinc depot, hypoglycemia becomes clinically manifest and

progressively more severe. If the hypoglycemic state is treated at this point with oral or parenteral administration of carbohydrate the blood sugar level may be raised to normal or close to normal levels, but this effect is very transient. The continuous liberation of insulin in the absence of glycogen stores in the body necessarily leads to recurrent hypoglycemia soon after each therapeutic administration of sugar until the protamine-zinc-insulin depot has been depleted.¹

Without adequate treatment, therefore, the hypoglycemia following overdosage with protamine zinc insulin is characterized by its intractability, severity and duration, and it is apt to lead to irreversible tissue changes (particularly in the brain⁴ and myocardium⁵) comparable to those found in prolonged anoxia.

Coma and vomiting have been a more prominent feature of the hypoglycemia due to protamine zinc insulin than of that caused by regular insulin.¹

A male diabetic patient who took 2000 units of protamine zinc insulin in a single dose afforded us the opportunity of observing some of the effects of such a large dose of insulin on the carbohydrate metabolism.

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CASE REPORT

The patient was a 63-year-old man who had had diabetes for about 10 years and who required 40 units of protamine zinc insulin daily. For the preceding few years he had also been treated for arteriosclerotic heart disease with anginal syndrome. For many years he had been unable to work because of poor vision. He became depressed, and 1 year previously he had attempted suicide with insulin.

On the morning of November 2, 1948, the patient received his usual injection of 40 units of protamine zinc insulin. At approximately 5 p.m. on the same day, the patient announced to his wife that he had a little while previously injected into himself the contents of "three bottles" of protamine zinc insulin with the intention of killing himself. The wife found the three empty bottles, two of 80 and one of 40 units per cubic centimeter (representing a total of 2000 units), the contents of which the patient claimed to have injected subcutaneously. At this time he showed no unusual symptoms. A doctor who was called at once declared treatment unnecessary.

During the night the patient had a few episodes of perspiration and apprehension, not different from the hypoglycemic symptoms occasionally experienced in the past. His wife treated them successfully with fruit juice and frequent feeding.

On the following morning he was taken to a hospital, where no sign of insulin reaction was found and, after several hours, he was transferred to the psychiatric division of Bellevue Hospital because of his repeated suicidal attempts. Immediately prior to his transfer he became apprehensive and started to perspire. He was given 40 cc. of 50 per cent glucose solution intravenously, and drank a cup of orange juice, immediate improvement followed.

On admission to Bellevue Hospital at 5 p.m. on November 3 he was fully conscious and oriented and asked for something to eat. He was sweating moderately and appeared very apprehensive but in no acute distress. The skin was cool, and the pulse very rapid and irregular. He was immediately given 50 cc. of 50 per cent glucose intravenously. Sweating and apprehension disappeared promptly, the pulse rate slowed, and he appeared comfortable and spoke rationally. Physical examination at this time showed a temperature of 98.4°F, a pulse of 64 and respirations of 16. The blood pressure was 130/68. Fundoscopy revealed diabetic retinopathy. The heart was enlarged. The chest was clear. The abdomen was soft. On both thighs were many injection marks. Neurologic examination was negative. The urine on admission was free of sugar and acetone.

The patient's course in the hospital was characterized by great difficulty in attaining and the inability to maintain a normal blood sugar level. This persisted for 6 days in spite of almost continuous oral and parenteral administration of huge amounts of carbohydrates. During this period there was a persistent tendency to lapse into hypoglycemia whenever the therapeutic efforts were relaxed.

Until 7 a.m. of the 2nd day—that is, during the first 38 hours after the insulin had been taken, the symptoms were mild and relatively easily controlled. This period included the first 14 hours at Bellevue Hospital, when 320 gm of carbohydrates was given—295 gm by mouth and 25 gm by vein.

After this 38-hour period had passed, however, the patient started to vomit and rapidly went into coma. At this time the blood sugar was less than 10 mg per 100 cc., 50 cc. of 50 per cent glucose was at once given intravenously and followed by an intravenous infusion of 12.5 per cent glucose in water. About 2 hours later the patient regained consciousness and was able to take food by mouth. He remained comfortable, except for a few episodes of sweating although the blood sugar did not rise above 33 mg per 100 cc. that afternoon.

The blood sugar was still 54 mg per 100 cc. at 10 p.m. on the 3rd day. During the 15-hour period from the onset of coma at 9 a.m. until midnight he received a total of 275 gm of glucose intravenously and 300 gm of carbohydrates orally in the form of sweetened fruit juices.

His condition became critical during the night and the following morning, when hypoglycemia was most profound and the largest amounts of carbohydrate he was to receive on any day were required. The intravenous infusion of

glucose had inadvertently been stopped, probably for about 1 hour before 2 a.m. At this time he was found vomiting and perspiring and rapidly lapsed into coma. After 50 cc. of 50 per cent glucose had been given intravenously he recovered quickly. The infusion was restarted at the same time. At 7:30 a.m. the infusion was stopped again. About 1 hour later the patient began to vomit, became deeply comatose, had a rapid, irregular pulse and developed pulmonary edema. The blood pressure was 180/80. He was again given 50 cc. of 50 per cent glucose intravenously but this time without response. The blood sugar of a specimen drawn a few minutes after the intravenous injection of glucose was reported as less than 10 mg per 100 cc. The serum potassium was 3.5 milliequiv per liter at this time. In view of the pulmonary edema it was believed that infusions should not be continued for the time being, and glucose was given in the form of a 50 per cent solution, 50 cc. at a time for a total of 260 gm between 9 a.m. and 9 p.m. In addition, 1800 cc. of milk and egg nog, containing 150 gm of carbohydrates, was fed to the patient through a Levine tube. He was rapidly digitalized and given a transfusion of 500 cc. of blood. After 4 hours of treatment, his coma lightened, but he remained confused and drowsy for the rest of the day. Pulmonary edema cleared gradually. During this period of generous oral and parenteral administration of glucose the urine remained almost consistently sugar free, and the blood sugar was 35 mg per 100 cc. at 12:40 p.m.

After 6 p.m. on the 4th day tube feeding was discontinued because of abdominal distention. Five hundred cubic centimeters of whole blood was given slowly. By 9 p.m. it was considered safe to resume glucose infusions, a 22 per cent solution was used for this purpose, and it was supplemented on two occasions by 50 cc. of 50 per cent solution injected intravenously. By midnight the urine showed a ++ test for sugar.

The patient had received a total of 920 gm of carbohydrate (680 gm by vein and 240 gm orally) during the preceding 24 hours. But shortly after midnight the urine was again sugar free, and restlessness and perspiration reappeared.

On the next morning he experienced mild hypoglycemic symptoms. At 8 a.m. the blood sugar was 50 mg per 100 cc. The 22 per cent intravenous glucose drip and the Levine-tube feedings were continued until 4 p.m., when the urine samples contained increasing amounts of sugar.

On the 5th day the patient's sensorium appeared clear, and he was able to take food and was started on a diet containing 180 gm of carbohydrate. His urine remained sugar free the rest of the day.

On the 6th day the patient again appeared drowsy most of the time. The blood sugar was found to be 30 mg per 100 cc. at 9 a.m., even though he had been receiving carbohydrate feedings during the night. During the day his condition remained unchanged and the urine was free of sugar on a diet containing 260 gm of carbohydrate.

He was, therefore, again started on intravenous 22 per cent glucose at 6 p.m. on the following day. Soon afterward he was found to be excreting increasing amounts of sugar (a +++ to ++++ test) in the urine. The infusion was stopped at 6 a.m. At 10 a.m. the blood sugar was 210 mg per 100 cc.

From the 8th day on, the patient was well oriented and took his full diet containing 180 gm of carbohydrate. During this period the urinary sugar varied from 0 to ++++, and the blood sugar remained around 200 mg per 100 cc.

On the 15th day it was decided to start the patient on insulin again, he received repeated small doses of regular insulin and was gradually returned to protamine zinc insulin.

Two weeks later the diabetes was well controlled on 40 units of protamine zinc insulin. The patient's physical and mental condition was quite satisfactory by this time, he was completely oriented and according to the statement of his wife had not changed in any way.

An electrocardiogram taken during the coma and pulmonary edema on the 3rd day showed sinus tachycardia (a rate of 144 per minute), with occasional premature ventricular contractions and elevated ST segments in Lead 2 and 3. Twelve days later, when the procedure was repeated, the rhythm was regular and the ST segments isoelectric.

In summary, after a single hypodermic injection of 2000 units of protamine zinc insulin this diabetic patient showed severe manifestations of hypoglycemia for 6 consecutive days with the greatest severity on the 3rd day. In this period he received almost 3000 gm of carbohydrate (1425 gm by

vein and about 1400 gm by mouth), but the urine remained sugar free most of the time and the blood sugar never exceeded 54 mg per 100 cc. Twelve days elapsed before it became necessary to reinstitute insulin therapy, although he had previously required daily injections of 40 units.

DISCUSSION

This case illustrates the problems created by an unusually great overdosage of protamine zinc insulin. The initial absence or paucity of symptoms in no way minimizes the seriousness of the situation. When a person is known to have received or is suspected of having received an excessive amount of protamine zinc insulin, he must be regarded as an emergency^{1, 7, 8} and kept under careful observation lest severe hypoglycemia develop abruptly and become increasingly difficult to control, if not fatal.

The experience with this patient also showed that prompt improvement of symptoms after carbohydrate administration must not give rise to a false sense of security. The response to the administration of glucose in such a case is bound to be quite transient since the liberation of insulin from the injected depot takes place over a long period, whereas the glycogen stores in the body are depleted during the early phases of hyperinsulinism. It is therefore of prime importance to administer a continuous supply of readily available carbohydrate to such patients.⁷ Oral feedings can be depended upon only if the patient remains fully conscious, a nurse is in constant attendance, and the patient does not vomit. If the patient is unconscious, full reliance cannot be placed on feeding through a Levine tube since gastric atony with retention may occur in this state.¹ Continuous intravenous drip infusion is therefore preferable during the critical phase. The attempt to give a sufficient amount of carbohydrate by this means is, of course, always fraught with the danger of flooding the circulation to a degree at which pulmonary edema results, as occurred in the case reported above. This difficulty can probably best be overcome by the use of a highly concentrated solution. A 22 per cent solution of glucose in water, occasionally supplemented by the further intravenous injection of 50 cc of a 50 per cent solution, was finally resorted to.

It should be emphasized that on the third day, during the most profound phase of hypoglycemia, a brief interruption of the parenteral supply of glucose led to a virtually complete disappearance of sugar from the circulating blood and to deep coma from which recovery was relatively slow. From the experiences in cases reported in the literature it may be assumed that serious organic damage would have resulted if such a degree of hypoglycemia had been allowed to persist longer.^{2, 4, 9, 10} Conversely, the patient's recovery without any demonstrable cerebral or cardiac damage may be attributed to the almost continuous maintenance of the blood sugar above levels injurious to brain

and heart by means of intravenous infusions and frequent feedings and by the intravenous administration of additional concentrated solutions of glucose whenever, in spite of all efforts, the blood sugar dropped below critical values. The recovery is the more remarkable since the patient had signs of pre-existent generalized arteriosclerosis with symptoms of circulatory (and particularly coronary) insufficiency. Other patients have been known^{4, 11, 12} to develop permanent brain damage of varying occasionally extreme severity after prolonged hypoglycemia, even though it resulted from far smaller doses of insulin.

It is generally recognized that the action of individual therapeutic doses of protamine zinc insulin may extend well beyond a twenty-four-hour period, even into the third day.⁸ In fasting patients single injections have maintained hypoglycemic levels for as long as forty-eight to seventy-two hours.¹¹ In animal experiments, a single injection of protamine zinc insulin has produced hypoglycemia of thirty hours' duration in rats and of three to five days' duration in dogs.¹⁵ The larger the dose given, the more prolonged the effect. The same statement, incidentally, holds for unmodified insulin, with which the duration as well as the intensity of the effect also varies in proportion to the size of the dose given.^{16, 17} To our knowledge, hypoglycemia of six days' duration, as reported above, has not been noted after a single injection of insulin. However, there is no basis for comparison, since there is no case on record in which such a large quantity of insulin was received in a single dose. The knowledge that the amount of insulin will directly determine the duration of its effect assumes practical importance whenever a large dose of protamine zinc insulin is given either in error or by design. Any prediction about the course of events in such cases, particularly regarding the duration of the critical period and the length of time during which continuous, vigorous therapy will be required, obviously cannot be based on experience with the customary doses of insulin, but must be estimated according to the amount administered. Periods of hypoglycemia of sixty hours, as observed by Aitkin,¹⁸ after 100 units of protamine zinc insulin, and of one hundred and forty-four hours, as seen in our case after 2000 units of protamine zinc insulin, could serve as two indexes that may be useful for calculation in cases of this kind.

The question may be raised why the patient received a transfusion of whole blood on the third day of treatment. The indication was based on Joslin's⁷ opinion that a transfusion of fresh blood may be able to supply the respiratory enzymes, which appear to be inhibited during hypoglycemia.¹⁹ It may also assist in the restoration of a disturbed electrolyte balance.

The electrocardiographic findings are noteworthy. During the episode of greatest hypoglycemia with coma and pulmonary edema, the findings included a sinus tachycardia (a rate of 144 per minute), premature ventricular contractions and definite elevation of the ST segments in Lead 2 and 3. At this time the blood potassium level was normal.^{20, 21} Twelve days later the ventricular rate was 64 per minute, and the ST segments isoelectric. These changes are at variance with those observed by others during hypoglycemia.^{22, 24}

SUMMARY

A case in which suicide was attempted with a single injection of protamine zinc insulin is reported. The patient had few symptoms during the first twenty-four hours but, in spite of vigorous and continuous treatment, developed increasingly severe hypoglycemia, with periods of coma on the second and third days, and recurrent manifestations of milder hypoglycemia, with a blood sugar of 30 mg per 100 cc up to the sixth day. During this period he received close to 3000 gm of carbohydrate and yet was unable to maintain or even approach a normal blood sugar level. The blood sugar, however, was kept above critical values (at 30 to 50 mg per 100 cc) most of the time, and the patient suffered no demonstrable permanent damage.

The possible causes for the delayed appearance of symptoms, the severity of the hypoglycemia and the difficulty in maintaining an adequate blood sugar level after an excessive dose of protamine zinc insulin are discussed. It is stressed that the duration of the hypoglycemic effect increases in proportion to the size of the dose. This fact may account for the extremely protracted course of hypoglycemia in the case reported, exceeding that in any other known case on record.

The therapeutic urgency in this type of case is emphasized, in particular, the necessity of continuous and prolonged intravenous administration of carbohydrate.

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vein and about 1400 gm by mouth), but the urine remained sugar free most of the time and the blood sugar never exceeded 54 mg per 100 cc. Twelve days elapsed before it became necessary to reinstitute insulin therapy although he had previously required daily injections of 40 units.

Discussion

This case illustrates the problems created by an unusually great overdosage of protamine zinc insulin. The initial absence or paucity of symptoms in no way minimizes the seriousness of the situation. When a person is known to have received or is suspected of having received an excessive amount of protamine zinc insulin, he must be regarded as an emergency case and kept under careful observation lest severe hypoglycemia develop abruptly and become increasingly difficult to control if not fatal.

The experience with this patient also showed that prompt improvement of symptoms after carbohydrate administration must not give rise to a false sense of security. The response to the administration of glucose in such a case is bound to be quite transient since the liberation of insulin from the injected depot takes place over a long period, whereas the glycogen stores in the body are depleted during the early phases of hyperinsulinism. It is therefore of prime importance to administer a continuous supply of readily available carbohydrate to such patients.⁷ Oral feedings can be depended upon only if the patient remains fully conscious, a nurse is in constant attendance and the patient does not vomit. If the patient is unconscious, full reliance cannot be placed on feeding through a Levine tube since gastric atony with retention may occur in this state.¹ Continuous intravenous drip infusion is therefore preferable during the critical phase. The attempt to give a sufficient amount of carbohydrate by this means is, of course, always fraught with the danger of flooding the circulation to a degree at which pulmonary edema results, as occurred in the case reported above. This difficulty can probably best be overcome by the use of a highly concentrated solution. A 22 per cent solution of glucose in water, occasionally supplemented by the further intravenous injection of 50 cc of a 50 per cent solution, was finally resorted to.

It should be emphasized that on the third day, during the most profound phase of hypoglycemia, a brief interruption of the parenteral supply of glucose led to a virtually complete disappearance of sugar from the circulating blood and to deep coma from which recovery was relatively slow. From the experiences in cases reported in the literature it may be assumed that serious organic damage would have resulted if such a degree of hypoglycemia had been allowed to persist longer.^{2, 4, 9, 10} Conversely, the patient's recovery without any demonstrable cerebral or cardiac damage may be attributed to the almost continuous maintenance of the blood sugar above levels injurious to brain

and heart by means of intravenous infusions and frequent feedings and by the intravenous administration of additional concentrated solutions of glucose whenever, in spite of all efforts, the blood sugar dropped below critical values. The recovery is the more remarkable since the patient had signs of pre-existent generalized arteriosclerosis with symptoms of circulatory (and particularly coronary) insufficiency. Other patients have been known^{11, 12} to develop permanent brain damage of varying occasionally extreme severity after prolonged hypoglycemia, even though it resulted from far smaller doses of insulin.

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The question may be raised why the patient received a transfusion of whole blood on the third day of treatment. The indication was based on Joslin's⁷ opinion that a transfusion of fresh blood may be able to supply the respiratory enzymes, which appear to be inhibited during hypoglycemia.¹⁹ It may also assist in the restoration of a disturbed electrolyte balance.

abdomen and buttocks. In desperation and not knowing where else to inject her insulin, she inquired about the possible harm that might come from injecting insulin into the lipoatrophic areas. There did not appear to be any serious objection to reinjection of these depressed areas. The patient

and has practically recovered from all her deformities.

We have since advised 6 other patients suffering from insulin lipoatrophy to inject their daily insulin doses repeatedly into the deepest portion of the depression and in all these cases have seen, in one



A



B

FIGURE 2 Case of Insulin Lipoatrophy in a Ten-Year-Old Boy Involving Both Buttocks
A shows appearance before treatment. B shows appearance six weeks after treatment. (Note almost complete recovery.)

returned one month later, and it was surprising to find that one atrophic area which the patient had not injected for two years, had, after repeated daily injections, filled out and returned to its normal configuration.

As a result of this experience, the patient has since reinjected all the scooped out depressions

month's time, striking complete recovery from the deformities.

SUMMARY

A method for the successful treatment of insulin lipoatrophy is briefly presented.

LIPOATROPHY FOLLOWING THE INJECTION OF INSULIN*

A Method of Control

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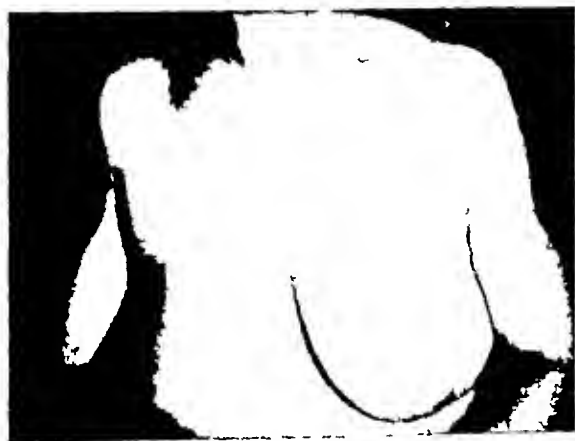
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AMONG the many problems that have arisen since insulin was introduced as an agent in the treatment of diabetes mellitus is one concerned with the development of local fat atrophy at the site of insulin injections. Although of relatively infrequent occurrence, the problem has always proved to be very distressing to the patient because of the considerable amount of disfigurement it produces.

Insulin lipoatrophy is a condition in which the subcutaneous fat disappears at the site of the insulin injection, leaving a depression in the skin (Fig

considered responsible are the cresols used as a preservative of insulin, alcohol and its denaturants used in sterilizing syringes and needles, injury to fat cells following the introduction of the hypodermic needle, possible lipolytic ferments present in insulin and possible nerve injury.

On the basis of the possibility that this condition might be an allergic phenomenon, some of the patients in our clinic were subjected to skin tests by the intradermal injection of various commercial brands of insulin. There was no uniformity in the reaction, some being negative and others mildly



A



B

FIGURE 1 Case of Insulin Lipoatrophy Involving Both Arms

A shows appearance before treatment. B shows appearance two months after treatment of the left arm. (Note the marked improvement, the right arm was used as a control and was not treated.)

1 and 2). It develops in some cases when the insulin is injected at the same site over a period of as little as four weeks. In other cases it may take months to appear. It may occur after the use of any type of insulin and is unrelated to the dosage and concentration.

The cause of this lipoatrophy is unknown. There has been no satisfactory explanation to account for the complication although several theories have been propounded. Among the possible factors

positive. Such reactions were also obtained in other diabetic patients who revealed no manifestations of lipoatrophy. It was therefore not possible to come to any conclusion regarding the existence of any unusual sensitivity in these cases. Furthermore, there are no experimental or clinical data available to shed any light on the mechanism responsible for the condition.

A successful method for the treatment of lipoatrophy is presented. This method was conceived as the result of a patient's suggestion. A young woman, twenty-three years of age, who had been diabetic since the age of twelve, had developed multiple areas of lipoatrophy on the arms, thighs,

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myocardium Quinidine concentrations in various tissues range from two to thirty-nine times the plasma concentration,^{113 114} and the level in auricular and ventricular muscle falls within this range.¹¹³ The time at which the highest quinidine concentration is reached, as well as the subsequent fall in concentration in cardiac muscle and other tissues, is correlated with plasma-level changes.¹¹³ These observations indicate a ready equilibrium between the plasma and tissues of the dog.

Few observations have been made in man of the extent to which quinidine is concentrated in various tissues. In normal persons receiving single and repeated doses of the drug the concentration of the quinidine in the cellular elements of the blood varies from 0 to 80 per cent of the plasma level.⁶⁴

Excretion and metabolic alteration The total urinary excretion of unaltered quinidine amounts to 5 to 20 per cent of the administered dose.^{64 112} Various metabolic products are recovered from urine but account for less than 5 per cent of the quinidine administered.^{112 115} In view of the essentially complete absorption, limited localization and limited excretion, it is apparent that the fate of quinidine in the body is primarily one of metabolic alteration.

Action on the Cardiovascular System in Animals

The main myocardial effects of quinidine are an increase in refractory period, thereby decreasing myocardial excitability, and a decrease in the rate of impulse conduction.^{116 117} Numerous observations have been made^{118 124} of the action of the drug on the cardiovascular system of various animals. Comparison is difficult, however, not only because of species difference but also because of different anesthetics and operative procedures and, above all, different doses of quinidine given intravenously at varying rates.

Recent studies in dogs¹²⁵ have described the cardiovascular changes as plasma quinidine levels are progressively raised by continuous intravenous infusions of the drug. The changes observed are closely correlated with the plasma concentration of quinidine. A fall in arterial blood pressure occurs with low plasma levels. As the concentration rises, sinus slowing appears and progresses and is accompanied by various electrocardiographic manifestations of interference with impulse formation in the sinoauricular node. There is finally a transition to auriculoventricular-node rhythm followed by intraventricular conduction block, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and death. These experimental observations cannot be applied directly to man. However, as discussed below, many of these cardiovascular effects seen in the dog may well have clinical counterparts.

Action on the Cardiovascular System in Man

Measurement of cardiac action and its relation to plasma concentration The end of an arrhythmia is an all-or-none phenomenon that cannot be measured, and other indexes must therefore be used to determine the action of quinidine on the heart. Changes in rate or in the electrocardiogram permit determination of the time factors in the action of the drug and, in a few cases, enable the intensity of action to be related to the size of the dose. Pertinent observations have been recorded on

The occurrence and degree of slowing of the auricular oscillations in the electrocardiograms of patients with auricular fibrillation^{64 113 126-128} and auricular flutter.^{7 133 134}

The occurrence and degree of prolongation of the QRS^{125 126} and QT¹²⁷ intervals of the electrocardiogram.

The effect on constant extrasystolic arrhythmias.^{135 139}

The slowing of the rate without restoration of normal sinus rhythm in patients with paroxysmal ventricular tachycardia.^{46 140 141}

The occurrence and degree of increase in the ventricular rate in undigitalized patients with auricular fibrillation.¹²⁶

The slowing of the rate without restoration of normal sinus rhythm in certain patients with paroxysmal auricular tachycardia.¹⁴²

The disappearance of the electrocardiographic abnormalities in the Wolff-Parkinson-White syndrome (short PR interval and wide QRS interval).¹⁴³

The development of bundle-branch block¹⁴⁴ in certain subjects with sinus tachycardia.

These studies following *oral* and *intramuscular* quinidine show that the time of onset of drug action, the time of maximum effect and the duration of action parallel closely changes in plasma concentration of quinidine described above.

Although plasma concentrations following *intravenous* quinidine are not known, the maximum cardiac effect as measured by auricular slowing in patients with auricular fibrillation and auricular flutter⁷ occurs almost immediately after completion of the intravenous injection and certainly within ten minutes. The maximum effect of 0.4 gm intravenously was approximately equivalent to 0.8 gm by mouth. These and other observations¹⁴⁵ indicate that the duration of action after intravenous administration is only a few hours.

It has been suggested^{113 132} that the relation between plasma concentration and cardiac action of quinidine is not strictly quantitative. However, the correlation is good and it seems valid, therefore, to use changes in the plasma concentration as a guide to changes in the intensity of action on the heart.¹⁰⁷

MEDICAL PROGRESS

MEASURES USED IN THE PREVENTION AND TREATMENT OF CARDIAC ARRHYTHMIAS (Concluded)*

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QUINIDINE (AND OTHER CINCHONA ALKALOIDS)

Quinidine is of recognized value in the prevention and treatment of various cardiac arrhythmias, such as paroxysmal ventricular tachycardia and paroxysmal auricular fibrillation. However, there is considerable disagreement about the exact indications and contraindications, the nature and frequency of toxic reactions, the routes of administration and the dosage schedules of the drug. Since there is so much confusion surrounding the use of quinidine, the pertinent available information has been assembled and is discussed in some detail.

Physiologic Disposition

Knowledge of the fate of quinidine in man has been obtained by sensitive, accurate and specific analytical methods developed in the past few years.⁹⁹⁻¹⁰⁵ The relation between oral dosage and the resulting plasma concentration has been studied, and information obtained on absorption, distribution, excretion and metabolic alteration, which combine to determine the level of quinidine in the blood.

Relation of oral dosage to plasma concentration Within fifteen minutes of a single oral dose of 0.2 to 1.0 gm. of quinidine sulfate the alkaloid can be detected in the plasma. Maximum levels are reached in one to three hours and may be maintained for two or three hours.¹⁰⁷⁻¹⁰⁹ The subsequent fall is at first fairly rapid and then slower. Approximately 50 per cent and 25 per cent of the peak value remain after eight and twelve hours respectively. At the end of twenty-four hours only a trace of quinidine can be demonstrated in the plasma. Average peak plasma concentrations after single doses of 0.2, 0.4, 0.6 and 1.0 gm. are, respectively, 0.8, 1.3, 2.0 and 2.7 mg. per liter.^{61-107, 110}

When the same dose of quinidine sulfate is administered at two-hour intervals—that is, at the time of the peak response to the preceding dose—the plasma concentration increases, but the increase becomes smaller and smaller with each successive dose, and the curve levels off after four or five doses.

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Presumably, at this point, the rate of absorption balances the combined rates of excretion and metabolic alteration.⁶¹⁻¹⁰⁷

When the same dose is repeated at intervals of six, eight or twelve hours, the peak level after several days is not significantly greater than that after the first dose. The maximum concentration is slightly lower when the doses are given every twelve hours than when they are given every six to eight hours, with the more frequent administration the concentration is maintained at a higher level in the period between peaks. When the size of the dose is increased, the height of the peak is raised appreciably.⁶¹⁻¹⁰⁷ The size of the individual dose is the most important factor in obtaining a high plasma level of quinidine.⁶¹ Cumulation is minimized by rapid elimination, and, therefore, the total daily dose and the total weekly dose are of little significance.

Relation of parenteral dosage to plasma concentration Limited information is available regarding the plasma concentration of quinidine following intramuscular administration.⁶¹ Initial absorption is more rapid than after oral administration; the peak level is no higher and does not occur significantly earlier. The rate of disappearance and the time required for complete disappearance from plasma are the same as those after oral administration. As would be expected on the basis of these findings, the plasma concentration following repeated intramuscular doses follows the same pattern as that after repeated oral doses.⁶¹

We are not familiar with any data on the plasma levels of quinidine following intravenous administration of the drug in man.

Absorption Quinidine is practically completely absorbed from the human gastrointestinal tract. After oral administration of repeated doses, less than 5 per cent can be recovered from the stools.¹¹¹⁻¹¹⁷ The rapidity with which the drug can be detected in the blood suggests that absorption must at least begin in the stomach. Absorption also occurs from the intestinal tract as evidenced by studies with enteric-coated tablets of quinidine sulfate, which, presumably, pass through the stomach unchanged. Peak plasma concentrations following the enteric-coated preparation are comparable to those observed after the administration of uncoated tablets.⁶¹

Distribution Distribution studies in dogs have shown no unusual concentration of quinidine in the

be given. Inasmuch as reactions to quinidine may be expected to occur within a few hours after a dose, a longer period of observation is not necessary. The appearance of severe untoward symptoms following the first of a proposed series of doses will serve as indication for modifying the dosage schedule. It is pertinent to emphasize the infrequency of serious reactions to quinidine.

Cardiac toxicity Although the potentially more serious toxicity of quinidine is related to its action on the heart, experience suggests that such toxicity is uncommon. The controversial problem of embolization in patients with chronic auricular fibrillation receiving quinidine will not be discussed here.⁶⁷ As mentioned above, increasing quinidine concentrations in dogs are associated with various manifestations of interference with normal cardiac impulse formation and conduction and, finally, with death. Although in some cases the relation to the drug is not definite, clinical counterparts of these experimental observations have been described in patients with various arrhythmias receiving quinidine. These include sinus arrhythmias,⁶⁷ auricular standstill,¹⁷⁴ auriculoventricular block,¹²⁶ bundle-branch block,¹⁴⁴ ventricular extrasystoles,⁵⁴ ¹²⁶ ¹⁶² ¹⁷⁶ ¹⁷⁷ ventricular tachycardia,⁵⁴ ⁶⁶ ¹²⁶ ¹⁶² ¹⁷⁶ transient ventricular fibrillation¹⁷⁸⁻¹⁸¹ and death.⁷ ⁵⁴ ¹⁸² ¹⁸³ In most cases these phenomena have been observed with moderate or large doses of quinidine. However, sufficient information is not available to indicate the likelihood of producing an untoward cardiac reaction in a given patient with a particular dose or plasma level of quinidine.

When quinidine is being administered, particularly in large doses, it is important to have some guide that will warn of approaching cardiac toxicity. It has been suggested that QRS lengthening of more than 25 per cent of the control value is not safe,¹³⁶ but more marked prolongation of the QRS complex has been witnessed without untoward effect when the situation required larger amounts of the drug.¹⁸⁴ When quinidine administration is associated with auricular standstill, bundle-branch block, a rise in ventricular rate, ventricular extrasystoles, ventricular tachycardia or transient ventricular fibrillation the drug should be stopped. Frequent electrocardiograms are thus helpful in controlling the therapeutic administration of quinidine, and correlation of electrocardiographic changes and plasma concentrations now being carried out¹⁸⁵ should give information of considerable value.

Contraindications

The only absolute contraindication to the administration of quinidine is a history of serious reaction to the drug.

Relative contraindications frequently mentioned include long-standing auricular fibrillation, bundle-branch block, auriculoventricular block, severe cardiac failure, marked cardiac enlargement, long-

standing valvular disease, subacute bacterial endocarditis, various acute infections and advanced age of the patient. The evidence that these factors increase the likelihood of cardiac toxicity is not conclusive, and they should not prevent use of the drug when there is a definite indication. Acute myocardial infarction has been considered both an indication and a contraindication. In such cases clinical experience with prophylactic doses of 0.2 to 0.3 gm of quinidine sulfate three or four times a day has not revealed any unusual incidence of toxic reactions.

Indications

Quinidine may be used effectively in the prevention and treatment of paroxysmal auricular fibrillation, paroxysmal auricular flutter, paroxysmal supraventricular tachycardia, paroxysmal ventricular tachycardia and ventricular extrasystoles. It has also been found to be of value in the treatment of certain cases of chronic auricular fibrillation when the arrhythmia may be causing recurrent embolization¹⁸⁶ or cardiac failure.¹⁸⁷

Quinidine is generally recognized as the drug of choice in paroxysmal ventricular tachycardia. In most other arrhythmias, however, other agents (Table 1) may be effective, and the relative value of quinidine cannot be accurately determined on the basis of the available evidence.

Preparations and Routes of Administration

Since it is promptly and almost completely absorbed from the gastrointestinal tract, quinidine is generally administered by mouth. Quinidine sulfate (*USP*) is available in 0.2-gm and 0.3-gm tablets for oral use.

Parenteral administration may be necessary when an acute arrhythmia is associated with collapse, unconsciousness, vomiting or other factors that make oral use impossible or absorption from the gastrointestinal tract uncertain. Injectable quinidine preparations are not readily available but may easily be prepared as stable aqueous solutions that can be stored in ampoules for emergency use. A 15 per cent solution of quinidine hydrochloride dissolved with the addition of 15 per cent antipyrine and 20 per cent urea¹⁸⁶ and a 15 per cent solution of quinidine lactate¹⁸⁸ have been used in man — the first intramuscularly, and the second both intramuscularly and intravenously. Quinidine acts more quickly intramuscularly than by the oral route, is at least as effective and may cause even fewer side reactions.¹⁸⁶ Quinidine has been used intravenously for therapeutic purposes,²⁵ ¹⁸⁹ ¹⁹³ but the advantage of the greatly increased speed of action is rarely important enough to warrant the greater danger of serious toxicity. The intramuscular route is the one of choice for parenteral administration.

Little information is available, as yet, on the relation between the plasma concentration of quinidine and the prevention or treatment of various arrhythmias. In 2 patients¹¹⁰ with recurrent auriculoventricular-node tachycardia, attacks were absent at plasma quinidine concentrations above 10 mg per liter but recurred when the levels were lower. The dose required to maintain this "critical" level was at least 0.2 gm of quinidine sulfate every four hours. In a small number of patients with various arrhythmias, restoration of normal sinus rhythm has occurred at levels ranging from 2 to 10 mg per liter.¹¹⁶

Comparison of the cardiac action of quinidine and other cinchona alkaloids. The action of quinidine from natural sources has been compared with that of other natural and synthetic cinchona alkaloids.^{126 128 130 137 147-149}

These various studies indicate that, with equal doses, natural and synthetic quinidine show the same activity and dihydroquinidine is more active, cinchonidine, cinchonine and quinine are less active. Inasmuch as quinine is occasionally used instead of quinidine in the treatment of cardiac arrhythmias, it is of practical importance to appreciate the quantitative difference in the action of the two drugs. In addition to the greater activity of quinidine on the basis of equal doses, it has been found that the maximum effect on the rate of the auricular oscillations in auricular fibrillation obtainable with increasing doses of quinine is never as great as that obtainable with increasing doses of quinidine.¹⁴⁷ Accordingly, the two drugs are not completely interchangeable. However, quinine has been used effectively in the treatment of paroxysmal auricular tachycardia,^{150 151} paroxysmal auricular fibrillation,¹⁵¹ paroxysmal auricular flutter¹⁵¹ and paroxysmal ventricular tachycardia.⁴⁶

Other cardiovascular effects. Various other cardiovascular effects of quinidine have been measured both in normal persons^{137 152} and in patients with cardiac disease,^{152 153} but the results are conflicting. After large single doses of quinidine sulfate by mouth, the heart rate has been found to show no significant changes^{137 152} or an increase¹⁵³, arterial blood pressure has been observed to fall¹⁵⁰ or to remain unchanged¹⁵³, cardiac output has shown no change in normal persons,¹⁵² a decrease or no change in cardiac patients without congestive failure¹⁵² and a rise from a previously low value in patients with cardiac decompensation.¹⁵² These last patients also showed a fall in arterial pressure and drop in a previously elevated right ventricular pressure. A fall in arterial pressure and a drop in peripheral resistance without change in cardiac output has been attributed to an action of quinidine on the peripheral vascular bed.¹⁵² The reported efficacy of quinidine in the treatment of angina pectoris^{154 155} suggests that the drug also causes dilatation of the coronary arteries.

Toxicity

Uncertainty about the toxicity of quinidine undoubtedly contributes to its limited use by many physicians. Although many questions regarding quinidine toxicity cannot be answered without further study, our experience and that of other clinicians indicate that serious side reactions are rare.^{127 128 137}

Quinidine, like quinine, has been labeled "a general protoplasmic poison."⁷⁶ The term is meaningless, however, and the toxicity of these substances for vertebrates is low.¹⁵⁸

*Cinchonism and other reactions.** In man, the most frequent side reactions are grouped under the term "cinchonism," the nature and severity of the symptoms varying, in general, with the size of the dose. In its mild form, this syndrome is not uncommon and includes nausea, abdominal discomfort, diarrhea, ringing in the ears and dizziness. If administration is interrupted, the symptoms usually subside promptly. On readministration, especially if the dose is increased more slowly,^{54 159} larger amounts may be given and higher plasma levels reached in the same patient without recurrence of symptoms. The little information available⁶⁴ suggests a lack of correlation between plasma concentration and the early symptoms of cinchonism. From 2.0 to 3.0 gm of quinidine sulfate has been administered repeatedly by mouth with the development of only minor side effects.^{160 161}

Certain persons may develop mild cinchonism even after a small oral dose of 0.2 gm. This mild, not uncommon but unimportant reaction may be inconstant in the same subject on different occasions and is no contraindication to further administration of quinidine.

Rarely, syncope,¹⁵⁹ convulsions,¹⁵⁹ sudden collapse¹⁶² and respiratory difficulty^{153 164} have been observed after a single small dose of quinidine. The evidence relating these phenomena to the administered quinidine is, however, inconclusive.

Reactions of an "allergic" nature have been described with quinidine but are rare. Skin rashes have been reported,^{137 165} but the best documented case reports concern the occurrence of fever¹⁶⁶ and thrombocytopenic purpura.¹⁶⁷ In each case the sensitivity has been an *acquired one, developing after one to three weeks of drug administration*. After the subsidence of the initial episode, readministration of a single small dose of quinidine has been followed by reappearance of the phenomena within two hours. In such cases quinine may be of value instead of quinidine, since persons sensitive to one are generally not sensitive to the other.^{166 168 172}

It has usually been recommended that, to detect sensitive persons, a small "test dose" of quinidine

*We have purposely avoided the term 'idiosyncrasy'. The literature on quinidine is needlessly confused by its use. *Webster's New International Dictionary of the English Language* defines 'idiosyncrasy' as 'a characteristic distinguishing an individual' and it may therefore properly be applied to many of these reactions.

prophylactic purposes, in patients whose repeated paroxysms of tachycardia have not been prevented by medical measures

Digitalis Glycosides

The main indication for the use of cardiac glycosides is congestive heart failure regardless of the rhythm. Digitalis preparations are widely used in patients with paroxysmal supraventricular tachycardia, auricular fibrillation and auricular flutter particularly if heart disease is present and the paroxysmal nature of the tachycardia is not clear. The mechanism of action of digitalis in preventing and stopping auricular arrhythmias is obscure. It is important to remember that paroxysmal tachycardia of ventricular origin is considered by many to represent a contraindication to digitalis therapy.

Choice of preparation The various considerations governing the selection of a digitalis glycoside have been the subject of a recent report.¹⁹¹ Numerous digitalis preparations have been used intravenously in the treatment of acute supraventricular arrhythmias. Although a great deal of emphasis has been placed on lanatoside C intravenously,^{59, 195, 196} there is no clear evidence that it accomplishes more than other digitalis preparations such as Digalen,⁵⁹ Digifolin⁶⁷ and ouabain.¹⁹⁷ Oral preparations have been used to prevent the recurrence of these arrhythmias.¹⁹⁵

Side effects The evidences of digitalis overdosage are well known. In the various studies with intravenous lanatoside C mentioned above, only occasional nausea and rare transient ventricular extrasystoles have been observed.

Efficacy in treatment of paroxysmal supraventricular arrhythmias Rapid restoration of normal rhythm has been observed after half to full "digitalizing" doses of cardiac glycosides intravenously in patients with paroxysmal auricular tachycardia, paroxysmal auricular fibrillation and paroxysmal auricular flutter. In many cases the effect occurred within five to ten minutes of the injection. In others, the change in rhythm occurred after a longer interval, up to twenty-four hours, and the relation to the drug was therefore not definite. In some cases ventricular slowing may be noted, although normal sinus rhythm is not restored. This may result in symptomatic improvement, and unless electrocardiograms are taken sinus rhythm may be thought to have returned.

In several cases of paroxysmal auricular tachycardia, Weisberger and Feil⁵⁹ found that carotid-sinus pressure, although previously ineffective stopped the attack immediately when applied after the administration of lanatoside C. This is in accord with the observation that digitalis increases the sensitivity of the carotid-sinus reflex.^{40, 60} A similar effect has been seen, as pointed out above in the first section after acetyl-beta-methyl-choline and neostigmine.

Efficacy in preventing paroxysmal supraventricular arrhythmias Tandowski¹⁹⁸ has maintained digitalization with 0.5 to 1.0 mg of lanatoside C by mouth daily in 8 patients with paroxysmal auricular flutter and auricular tachycardia. Only three attacks occurred during a fifteen-month period of treatment compared to twenty-four during a twelve-month period prior to digitalization. Although the observations were not completed by the omission of digitalis to determine if the frequency of attacks increased the results are consistent with our own experience.

Summary Digitalis preparations are of value in the prevention and treatment of paroxysmal supraventricular arrhythmias. The intravenous route of administration has been found particularly useful in stopping paroxysms of tachycardia. These substances can be given safely in therapeutic doses and may, of course, be of value for associated cardiac failure.

Magnesium Sulfate

High concentrations of magnesium ion depress the cardiac conduction system and heart muscle. As the serum concentration of magnesium ion is increased in animals, prolongation of the PR and QRS intervals is observed, the cardiac rate decreases and cardiac arrest occurs.^{199, 200} Stanbury²⁰¹ has shown that the magnesium ion has a blocking action on sympathetic ganglions, the cardiac slowing may therefore be related to this effect as well as to direct cardiac depression. In dogs magnesium sulfate has been found to be of some value in preventing ventricular arrhythmias due to mercurial diuretics.²⁰²

Although magnesium sulfate has been found to be of value in various types of paroxysmal tachycardia,²⁰³⁻²⁰⁷ similar doses have little effect on the normally beating human heart.^{203, 208}

Method of administration Intravenous doses range from 10 to 20 cc of a 10 to 30 per cent (in most cases, 20 to 25 per cent) solution of magnesium sulfate in distilled water.

It appears that the concentration of the drug reaching the heart is the important factor, accordingly, intravenous injection is accomplished in twenty to thirty seconds. If there is any effect on the arrhythmia, it occurs at once.

Side effects and contraindications An unpleasant though transient generalized feeling of intense heat and an associated drop in blood pressure (20 to 30 systolic) may occur^{204, 206} immediately after the intravenous administration of magnesium sulfate. There may also be perspiration, flushing, dizziness, frequently nausea but rarely vomiting and a transient feeling of generalized weakness. Ventricular premature beats may be observed for a short period.²⁰⁶ It has been suggested²⁰⁶ that magnesium sulfate should not be used in the presence of marked myocardial damage, intraventricular-conduction de-

Dosage Schedules

Schedules of quinidine administration for prophylactic and therapeutic purposes differ considerably and must be established in accordance with the requirements of a particular case.

Prophylactic administration In many patients with recurrent paroxysms, attacks are so infrequent and mild that continued administration of quinidine is not warranted. Prophylactic administration is instituted only when paroxysms of tachycardia tend to recur frequently or when single paroxysms are serious because of their severity or their nature (for example, ventricular tachycardia). In such patients individualization of dosage is important; initial doses of 0.2 gm. three times a day, if inadequate to prevent recurrence of the paroxysms, may be followed by larger doses and more frequent administration; 1.0-gm. doses have been given repeatedly for long periods.⁵¹ In certain persons it may be necessary to arrange the doses to minimize the interval between the last night and the first morning dose. In these cases enteric-coated tablets may be of value. Because of the rapidity with which quinidine is eliminated, long-continued administration carries no danger of cumulative toxicity, and the drug has been administered regularly for years without ill effect.^{51, 135}

Quinidine is often used to prevent the occurrence of arrhythmias, which may develop during acute myocardial infarction and thoracic surgery. In patients with acute myocardial infarction 0.2 to 0.3 gm. is customarily administered three or four times during the day. In view of the unpredictability of the occurrence of these arrhythmias, the efficacy of such prophylaxis is difficult to evaluate. When necessary, the size of the individual dose can be increased to 0.4 or 0.6 gm.

In patients undergoing thoracic surgery, quinidine is often used prophylactically during the operation and the early postoperative period. A dose of 0.4 to 0.6 gm. is administered by mouth or intramuscularly one or two hours before the operation and continued every six to eight hours for a few days postoperatively.

Therapeutic administration In the treatment of an acute arrhythmia the urgency of the situation will influence considerably the manner in which quinidine is administered. Effective therapeutic results can be achieved with oral administration, but when necessary the drug may be given intramuscularly. In most cases, with oral or intramuscular routes, doses are repeated at intervals of about two hours. This permits observation of the maximum beneficial and untoward effect of each dose. When a more rapidly increasing effect is required, the drug may be given every hour.

An initial dose of 0.2 to 0.6 gm. is commonly used, the larger amount being given in the more urgent situation. A favorable response is mani-

fested by definite cardiac slowing, rise in blood pressure, decrease in symptoms or improvement in the patient's general condition. If this occurs after the first dose, the same dose may be repeated every two hours as long as improvement continues. Usually, if normal sinus rhythm has not returned after three or four such doses, the size of the dose is increased by 0.1 or 0.2 gm. This dose may then be given three or four times before it is increased further.

If a favorable response is not seen after the first dose, the second dose should be 0.1 or 0.2 gm. larger than the first, and subsequent doses may similarly be increased. In most cases individual doses do not often need to be raised above 1.2 gm. before normal rhythm is restored.

In the treatment of chronic auricular fibrillation many different dosage schedules have been recommended. As utilized by us, the drug is administered every four hours, and the size of the individual dose increased by 0.2 gm. every twelve to twenty-four hours. Ample time is therefore afforded to observe the effect of a particular level of quinidine. In the past, the drug has too often been declared ineffective in this disorder after inadequate trial because arbitrary fixed schedules have been followed.

Summary

Physiologic and pharmacologic data accumulated in the past few years, although providing a more rational basis for the use of quinidine, are as yet incomplete. Quinidine is of outstanding value in the management of paroxysmal ventricular tachycardia; its relative efficacy in other paroxysmal arrhythmias has not been established.

MISCELLANEOUS MEASURES

Grouped in this section are other drugs that have been used in the prevention and treatment of cardiac arrhythmias. Several — for example, procaine, quinacrine and Metrazol — are of value for other clinical conditions, and others — such as morphine, Paredrine and Neo-Synephrine — are useful in the treatment of certain effects consequent to a rapid heart rate, such as pain, restlessness, hypotension and peripheral vascular collapse. These drugs are listed in Table 1. Further studies of these drugs may lead to better treatment of cardiac arrhythmias. It is likely that some drugs on the list have been unjustifiably credited with prophylactic or therapeutic value. The establishment of rational methods for using older agents in these disorders may be as important as, if not more important than, the development of new ones. As pointed out above in the first two sections of this review, the multiplicity of measures used in cardiac arrhythmias has resulted in inadequate study of most of them.

The various surgical procedures that have been carried out on the sympathetic nervous system (Table 1) have had a very limited use, generally for

prophylactic purposes, in patients whose repeated paroxysms of tachycardia have not been prevented by medical measures

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fects or gallop rhythm. Since magnesium is excreted largely by the kidneys,⁷⁶ it should be used with care in the presence of renal failure.²⁰³

Efficacy in treatment of various arrhythmias. Beneficial action has been reported²⁰³⁻²⁰⁷ in paroxysmal supraventricular tachycardia, paroxysmal ventricular tachycardia and ventricular premature beats due to digitalis. The effect, especially in the digitalis-induced extrasystoles, has sometimes been only transient. Increase in auriculoventricular block has been seen in auricular flutter but, in general, no beneficial effect has been observed in this arrhythmia or in auricular fibrillation.

Summary. Magnesium sulfate has been less widely used in the management of paroxysmal tachycardias than the digitalis glycosides and other agents. Its short duration of action makes its prophylactic use impractical. Therapeutically, it appears to be effective in many cases, but its use is associated with transient unpleasant side effects.

SUMMARY OF THERAPEUTIC PROGRAMS IN THE ARRHYTHMIAS

The large number of available measures for the management of paroxysmal arrhythmias poses a considerable problem for the physician. It is pertinent, therefore, that we summarize our own programs in the various arrhythmias.

Paroxysmal Supraventricular Tachycardia

Carotid-sinus and eyeball pressure are simple, safe means of reflex vagal stimulation, effective often enough to warrant their trial as the initial procedures in all cases. These measures, particularly carotid-sinus stimulation, should be repeated frequently along with some of the miscellaneous measures discussed above.

If these simple measures fail, sedation (by barbiturates) and rest are often associated with restoration of normal rhythm. In the absence of pulmonary congestion, angina pectoris, congestive failure, vascular collapse, cerebral manifestations or embolism this nonspecific therapy may be continued for twenty-four to forty-eight hours or longer before other measures are used. Neostigmine, Neosynephrine, Paredrine or acetylcholine may then be administered particularly in young persons with normal hearts. If parasympathomimetic drugs are used (such as Neostigmine) reflex vagal stimulation should be repeated. Although previously ineffective carotid-sinus stimulation a few minutes after administration of these drugs often stops an attack. Although ipecac is unpleasant because of the necessary association of vomiting with its beneficial action it is safe, and we have used it successfully. In the patient with cardiac disease, especially if congestive failure is present and the simple reflex measures mentioned above have failed, digitalis is the drug of choice. Quinidine is of value in many cases refractory to these measures.

If the tachycardia persists, other agents reported to be of value, such as magnesium sulfate, potassium salts, procaine and quinacrine may be tried.

Paroxysmal Auricular Fibrillation and Paroxysmal Auricular Flutter

It should be emphasized that in most cases sedation and rest alone may be accompanied by reversion to normal sinus rhythm. If not, and in the presence of symptoms, the choice of therapy lies between quinidine and digitalis. In young persons without heart disease we use quinidine. In the presence of heart disease or congestive failure, or both, digitalis is the drug of choice.

Chronic Auricular Fibrillation

When treatment is necessary, digitalis is used. In some unusual cases of congestive failure or embolism due to arrhythmia, quinidine has been used successfully.

Ventricular Extrasystoles

The avoidance of tobacco and coffee and the use of sedatives are very often beneficial. If not, quinidine, in doses outlined above, may be used effectively.

Paroxysmal Ventricular Tachycardia

Quinidine is the drug of choice if specific treatment is necessary. The dosage schedules have been given above. In refractory cases, other drugs, such as magnesium sulfate, potassium salts, diethylaminoethanol and morphine, may be tried.

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fects or gallop rhythm. Since magnesium is excreted largely by the kidneys,⁷⁶ it should be used with care in the presence of renal failure.²⁰³

Efficacy in treatment of various arrhythmias. Beneficial action has been reported^{203, 207} in paroxysmal supraventricular tachycardia, paroxysmal ventricular tachycardia and ventricular premature beats due to digitalis. The effect, especially in the digitalis-induced extrasystoles, has sometimes been only transient. Increase in auriculoventricular block has been seen in auricular flutter but, in general, no beneficial effect has been observed in this arrhythmia or in auricular fibrillation.

Summary. Magnesium sulfate has been less widely used in the management of paroxysmal tachycardias than the digitalis glycosides and other agents. Its short duration of action makes its prophylactic use impractical. Therapeutically, it appears to be effective in many cases, but its use is associated with transient unpleasant side effects.

SUMMARY OF THERAPEUTIC PROGRAMS IN THE ARRHYTHMIAS

The large number of available measures for the management of paroxysmal arrhythmias poses a considerable problem for the physician. It is pertinent, therefore, that we summarize our own programs in the various arrhythmias.

Paroxysmal Supraventricular Tachycardia

Carotid-sinus and eyeball pressure are simple, safe means of reflex vagal stimulation, effective often enough to warrant their trial as the initial procedures in all cases. These measures, particularly carotid-sinus stimulation, should be repeated frequently along with some of the miscellaneous measures discussed above.

If these simple measures fail, sedation (by barbiturates) and rest are often associated with restoration of normal rhythm. In the absence of pulmonary congestion, angina pectoris, congestive failure, vascular collapse, cerebral manifestations or embolism this nonspecific therapy may be continued for twenty-four to forty-eight hours or longer before other measures are used. Neostigmine, Neo-Synephrine, Paredrine or acetylcholine may then be administered, particularly in young persons with normal hearts. If parasympathomimetic drugs are used (such as Neostigmine) reflex vagal stimulation should be repeated. Although previously ineffective, carotid-sinus stimulation a few minutes after administration of these drugs often stops an attack. Although ipecac is unpleasant because of the necessary association of vomiting with its beneficial action, it is safe, and we have used it successfully. In the patient with cardiac disease, especially if congestive failure is present and the simple reflex measures mentioned above have failed, digitalis is the drug of choice. Quinidine is of value in many cases refractory to these measures.

If the tachycardia persists, other agents reported to be of value, such as magnesium sulfate, potassium salts, procaine and quinacrine may be tried.

Paroxysmal Auricular Fibrillation and Paroxysmal Auricular Flutter

It should be emphasized that in most cases sedation and rest alone may be accompanied by reversion to normal sinus rhythm. If not, and in the presence of symptoms, the choice of therapy lies between quinidine and digitalis. In young persons without heart disease we use quinidine. In the presence of heart disease or congestive failure, or both, digitalis is the drug of choice.

Chronic Auricular Fibrillation

When treatment is necessary, digitalis is used. In some unusual cases of congestive failure or embolism due to arrhythmia, quinidine has been used successfully.

Ventricular Extrasystoles

The avoidance of tobacco and coffee and the use of sedatives are very often beneficial. If not, quinidine, in doses outlined above, may be used effectively.

Paroxysmal Ventricular Tachycardia

Quinidine is the drug of choice if specific treatment is necessary. The dosage schedules have been given above. In refractory cases, other drugs, such as magnesium sulfate, potassium salts, diethylaminoethanol and morphine, may be tried.

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DIFFERENTIAL DIAGNOSIS

DR JOHN CRAWFORD The important facts seem to be the following: this five-month-old infant was entirely well until seven days before death. For one week he had had diarrhea amounting to eight stools daily, which were liquid and yellow at first, becoming green but without blood.

In the infant under one year of age diarrhea is a frequent symptom of extra-enteral infection. Nowadays, with milk pasteurization and good refrigeration, diarrhea due to true enteral infection is becoming less and less common. I think we may guess that the child had a parenteral infection, probably an upper respiratory infection, with diarrhea as the chief symptom.

Apparently, this mother of three children had had previous experience with infantile diarrhea and immediately began limitation of solid food. When this failed to alleviate the difficulty the family physician was called. We are not told what he found. My guess is that he found evidence of a pharyngitis or otitis media, for which he prescribed sulfonamides. He also prescribed bismuth and paregoric, which sometimes are effective in quieting a mild diarrhea but rarely in severe diarrhea.

On the day before death the infant began to refuse fluids, and it was said that his urine was pink, this, from subsequent findings, apparently being due to blood. His condition rapidly deteriorated, for the next day he was taken to a hospital, where he was found to be in a critical condition.

The physical examination at that hospital showed a drowsy, dehydrated infant, with a temperature of 103°F and an upper respiratory infection. Edema of the penis and scrotum was noted, without edema elsewhere. The urine was grossly bloody. Evidently no casts were seen. We are told that the urine contained 90 mg of albumin per 100 cc. This is not a great deal: the commonly used heat and acetic acid test would be interpreted as + to ++ with this degree of albuminuria. We do not know whether the urine was concentrated or dilute.

A considerable anemia was present. The prematurely born infant of five months ordinarily has about 10 gm of hemoglobin. This infant had 8.7 gm. I would interpret this figure to represent a marked deviation from normal in view of the clinical dehydration. Serum chemical analyses revealed a nonprotein nitrogen of 37.7 mg per 100 cc, a startlingly high figure; the blood sulfonamide level was only 1.4 mg per 100 cc.

In short, the infant was obviously critically ill. He was given emergency treatment consisting of blood to correct the anemia, fluid to combat dehydration and penicillin for infection, and was then referred with all dispatch to this hospital.

Following arrival here we learn little more to help in making the diagnosis before death. The child was in collapse, he had episodes of convulsive

movements. One observer thought that he had hypertension. He died only two hours after admission.

There are several diagnoses to be considered. The older texts say that syphilitic nephritis is the commonest hemorrhagic nephritis in infants under one year of age. In this part of the country congenital syphilis is seen with ever-diminishing frequency. I would expect the protocol to mention syphilis in the mother or a positive blood test in the child if this merited further consideration.

A sulfonamide tubular nephrosis due to crystal formation might be considered, but there are several points against this diagnosis. The physician treating the infant wisely used a mixture of three sulfonamide drugs so that the antibacterial effect would be proportional to the sum of the serum concentrations of each, and yet the danger of renal precipitation in the face of diarrhea would be minimal since the solubility of each sulfonamide component is independent of the other two in the renal tubular fluid. Furthermore, the blood sulfonamide level of 1.4 mg per 100 cc, obtained twenty-four hours or less after the last dose in an oliguric patient, is indicative of conservative use of the drug.

The child might have had a sulfonamide-sensitivity nephritis. This would be unexpected so soon after the initial dose. We have no history of prior sulfonamide administration, which might account for an accelerated reaction.

Acute hemorrhagic nephritis is a definite possibility. We have evidence of a preceding respiratory infection, which might well have been streptococcal. We have hematuria, oliguria, nitrogen retention and possibly hypertension with encephalopathy.

To make this diagnosis I should like to have the report of granular casts in a concentrated urine. Such an extremely high nonprotein nitrogen is unusual. There was less albuminuria than I would expect. Moreover the disease itself, while very common in childhood, is distinctly rare in the infant under six months. I cannot rule out acute hemorrhagic nephritis, but I do not believe that it fits the clinical picture as well as another diagnosis.

Although a transfusion nephrosis seems unlikely, since the symptoms were well established before the giving of blood, it might be mentioned that there is some evidence that transfusion of blood in which the plasma complement titer is high may aggravate an already existing glomerulonephritis.

The diagnosis I favor here is that of "hemorrhagic infarction of the kidney." Quite a large number of cases have been reported in infancy, particularly as a complication of diarrheal episodes. Barenberg¹ and Hepler² have reported a considerable number of cases in infancy.

I would suppose that the sequence of events in this infant was as follows: seven days before death

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35421

PRESENTATION OF CASE

A five-month-old-male infant was admitted to the hospital because of diarrhea

The patient was born prematurely of a pregnancy that was complicated by kidney disease diagnosed as pyelitis. However, the baby's development had been entirely normal, and three siblings were living and well. A week before admission he began to have diarrhea that did not respond to limitation of solid foods, passing about eight liquid stools a day, which were yellow at first and later green. Two days before admission a physician prescribed a mixture of triple sulfonamides, bismuth and paregoric of which an unknown amount was taken over the next twenty-four hours. On the following day the fluid intake was only 5 ounces, and the mother

noted that the baby's urine was pink. On the day of admission the baby was seen at another hospital, where physical examination showed a drowsy, dehydrated infant with a temperature of 103°F and a pink diaper stain. There was edema of the penis and scrotum and a mild pharyngitis. The urine was packed with red cells and contained 90 mg per 100 cc of albumin. The hemoglobin was 8.7 gm per cent, the red-cell count 2,700,000, and the white-cell count 11,500, with 66 lymphocytes, 32 per cent mature neutrophils, 1 per cent stab cells, and 1 per cent basophils. The blood was type O and Rh+. The nonprotein nitrogen was reported as 377 mg per 100 cc, the sulfonamide level was 1.4 mg per 100 cc. He was given a 180-cc infusion of 5 per cent glucose in physiologic saline solution, 80 cc of whole blood and 300,000 units of procaine penicillin, and referred to this hospital.

On admission the baby was pale, comatose and gasping. The eyes were turned up, and there were convulsive movements of the right arm. Coarse bubbling rales were heard bilaterally. The heart rate was 140 without murmurs. The systolic blood pressure was thought to be 140 by one observer. A blood culture was later reported as negative.

Oxygen and artificial respiration were begun immediately, and after some thirty minutes the baby improved. However a second left-sided convulsion followed, subsiding without treatment. He was then given 0.16 mg of Cedilamid intravenously and 15 mg of phenobarbital subcutaneously. At this point a third convulsion occurred, and the baby stopped breathing.

In spite of artificial respiration, oxygen, caffeine and sodium benzoate intravenously and 0.5 cc of epinephrine injected into the heart, the infant died two hours after admission to the hospital.

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I would suppose that the sequence of events in this infant was as follows: seven days before death

he had contracted an upper respiratory infection that resulted in moderate diarrhea. The day before entry, possibly as a result of factors such as dehydration and diminished blood volume, thromboses began to form in the small vessels of the kidneys, with resultant hematuria and oliguria. This process, once initiated, extended very rapidly and may have involved not only the blood vessels of the kidney but also those of the pelvis, giving rise to the peculiar edema of the penis and scrotum observed on physical examination. The extravasation of blood into the infarcted renal tissues resulted in the marked anemia and contributed to the extreme elevation of the nonprotein nitrogen. When this condition is bilateral or goes unrecognized for any length of time, collapse and death soon result.

Campbell and Matthews³ emphasize that the diagnosis should be made clinically on the basis of the history and on the physical finding of firm flank masses. However, Barenberg,¹ describing 5 cases in infants, was unable to palpate a swollen kidney in any of them.

In summary, then, the protocol suggests to me either acute hemorrhagic nephritis following a streptococcal respiratory infection or so-called "acute hemorrhagic infarction" of the kidney. Of these two diagnoses, the latter seems to fit the few facts outlined in the protocol somewhat better than the former.

CLINICAL DIAGNOSIS

Acute hemorrhagic nephritis

DR CRAWFORD'S DIAGNOSES

Diarrhea due to acute pharyngitis
Dehydration secondary to diarrhea
Acute hemorrhagic infarction of kidneys

ANATOMICAL DIAGNOSES

Ischemic necrosis of kidneys
Pulmonary edema
Petechial hemorrhages in brain

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY: Dr Crawford's prediction is, I think, essentially correct. The only major lesion at autopsy was found in the kidneys, which were markedly enlarged and grossly hemorrhagic. Microscopical examination showed a picture, which to me is unfamiliar in infancy, of extensive necrosis, predominantly in the cortex, though some foci were present in the pyramids. This necrosis was most marked in the tubules and was present to a less degree in the glomeruli. We could find no thrombosed vessels anywhere in the kidneys. There were a few small areas in which complete infarct-like necrosis with interstitial hemorrhage was present. The majority of the kidney showed a much less severe, degenerative process from which one would, I think, assume that recovery might

have been possible. The major part of the blood evident on gross examination lay in the lumen of the tubules, giving evidence that there had been massive leakage of blood through the glomerular tufts, and, quite often, Bowman's capsule was found acutely distended with red cells.

Other parts of the body showed what I think were only secondary features: extensive pulmonary atelectasis and edema and multiple, minute petechial hemorrhages throughout the brain — a not too uncommon complication of uremia.

DR ALFRED KRANES: How does the picture differ from bilateral cortical necrosis?

DR MALLORY: It is very similar, and that is, in fact, the diagnosis that I made.

DR KRANES: Does that occur in infants?

DR MALLORY: Dr Crawford knows more about that than I do, and I would like to ask him.

DR CRAWFORD: I tried to emphasize that I put "acute hemorrhagic infarction" in quotation marks because I did not think it was a good descriptive term. In the pediatric literature "acute hemorrhagic infarction" is used to describe a condition that seems to be very similar to the "acute cortical necrosis" of the adult literature. The terms probably refer to the same disease.

DR MALLORY: I think there is very little doubt that it is the same condition. My only hesitancy in calling it acute cortical necrosis was the fact that there was some involvement of the pyramids, which is unusual, at least in the adult cases of cortical necrosis. Cortical necrosis is seen most commonly in pregnancy, but it can occur in other conditions, and in the male as well as the female. It has been seen in association with a variety of infections and occasionally follows shock and burns. Vascular thrombosis may or may not be present and may well be secondary rather than primary. I suspect that this is also true of the lesion described as "renal thrombosis with infarction" in the pediatric literature.

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CASE 35422

PRESENTATION OF CASE

First admission. A fifty-five-year-old Greek barber was admitted to the hospital because of swelling of the legs, genitalia and abdomen.

The patient was well until some eight years before admission, when he first began to notice evening ankle edema, which subsided on rest at night. This persisted until about two months before entry, when the swelling became progressively worse and no longer cleared by morning. This was followed

soon afterward by swelling of the genitalia and, to a lesser extent, the abdomen. During the month before admission he had experienced a sense of discomfort in both upper quadrants, with sharp pain on deep breathing. He also noticed a three-flight exertional dyspnea without orthopnea. There was no history of nausea or vomiting, hematemesis, melena or recent jaundice. His appetite was good, but he had lost about 15 pounds in weight during the last eighteen months. The patient gave a history of painless jaundice some twenty-five years before. He stated that he drank two or three glasses of wine a day. One week before admission the patient was seen in the Outpatient Clinic where diuretics were administered with marked diminution of swelling.

The patient had a penile lesion twenty years before and was treated with thirty intravenous injections.

Physical examination revealed a well developed and well nourished man in no acute distress. There was slight icterus of the skin and scleras but no spider angiomas. The chest was clear except for a few rales in the right base. The liver edge was palpated two or three fingerbreadths below the right costal margin, and the spleen two fingerbreadths below the left costal margin. There were many prominent veins over the abdomen and shifting dullness without a fluid wave. Tenderness was present in both upper quadrants. There were several external hemorrhoidal tabs, and the prostate was slightly enlarged. The lower legs showed a ++ edema, varicosities and pigmentation of the skin.

The temperature was 99°F, the pulse 80, and the respirations 20. The blood pressure was 95 systolic, 60 diastolic.

The urine was yellow and cloudy and had a specific gravity of 1.012. It gave a +++ test for albumin but contained no bile. There were 20 to 30 white cells per high-power field in the sediment. A urine smear showed rare clusters of gram-positive cocci and a urine culture grew *Staphylococcus albus*. The blood hemoglobin was 10 gm, and the white-cell count 3800, with 56 per cent neutrophils. The blood nonprotein nitrogen was 40 mg, and the total protein 7.11 gm per 100 cc, with an albumin of 3.55 gm and a globulin of 3.56 gm. The fasting blood sugar was 124 mg per 100 cc, and the cephalin flocculation test was ++ and ++++ in twenty-four and forty-eight hours, the thymol turbidity was 13.5 units, the cholesterol 241 mg and cholesterol esters 115 mg per 100 cc. The prothrombin time was 15 seconds (normal, 15 seconds). The serum van den Bergh reaction was 0.6 mg per 100 cc direct and 0.8 mg indirect, and the alkaline phosphatase 5.2 units per 100 cc. A bromsulfalein test showed 36 per cent retention of the dye. A blood Hinton test was positive.

A gastrointestinal series was negative. No varices were identified. The spleen was enlarged, and a

roentgenogram of the chest showed only slight prominence of the left ventricle. A phenolsulfonephthalein test showed normal excretion, and a urea-clearance test gave specific gravities of 1.012, 1.015 and 1.015. The patient was advised concerning a high-calorie, high-protein, low-sodium diet and was discharged on the ninth hospital day somewhat improved. During this period in the hospital daily afternoon temperature rose to about 100°F. Four separate urine specimens showed 5 to 40 white cells per high-power field in the sediment and had specific gravities that ranged from 1.012 to 1.015. On two occasions the urine contained occasional granular and hyaline casts.

Final admission (approximately two months later). In the interval the patient noted progressive weakness and loss of appetite. One month before entry swelling of the legs, genitalia and abdomen again became marked despite diuretic therapy. An abdominal paracentesis was performed by a physician, with the removal of a considerable amount of fluid, but the abdominal swelling soon recurred. His skin became increasingly more jaundiced, and he had experienced nausea and vomiting during the three days before admission.

The findings on physical examination were essentially the same as those at the time of the previous admission, with the addition of pulsating neck veins.

The temperature was 99°F, pulse 80, and the respirations 20. The blood pressure was 136 systolic, 76 diastolic.

The urine had a specific gravity of 1.020 and gave a ++ test for albumin and bile. The sediment contained 2 or 3 red cells and 6 to 8 white cells and many hyaline and granular casts per high-power field. The blood hemoglobin was 9.5 gm and the white-cell count 6000, with 74 per cent neutrophils. The red cells showed moderate anisocytosis and hypochromia. The blood nonprotein nitrogen was 35 mg, and the total protein 7.85 gm per 100 cc, with an albumin of 3.08 gm and a globulin of 4.77 gm. The cephalin flocculation test was +++ and ++++ in twenty-four and forty-eight hours. The serum van den Bergh reaction was 6.0 mg per 100 cc direct and 8.4 mg indirect, and the alkaline phosphatase was 5.4 units per 100 cc. The prothrombin time was 21 seconds (normal, 15 seconds).

The patient became increasingly more drowsy and icteric, ate little and vomited frequently. The edema did not respond to the usual therapy. On the eighth hospital day after being comatose for twenty-four hours, he died.

DIFFERENTIAL DIAGNOSIS

DR JACOB LERMAN. I should like to know if mention is made of treatment for the urinary infection during the first admission.

DR TRACY B MALLORY There is no notation about therapy for pyelitis

DR LERMAN The initial symptoms could be explained either by right-sided heart failure or by the beginning of portal obstruction or portal cirrhosis. The slow development of edema, first in the legs and then in the abdomen, and finally the enlargement of the liver suggest the course of events that one sees in right-sided failure. However, he had no symptoms of right-sided failure. Mention is made of three-flight dyspnea. That is normal for all of us. There was no respiratory distress on examination. In spite of the type of onset, there was no evidence of cardiac involvement. He had an episode of painless jaundice, which does not seem to have much bearing on the problem. No doubt the intake of wine is of importance in this particular eastern Mediterranean race. He had evidence of acquired syphilis as indicated by a positive blood Hinton reaction, it may have played an important role.

On physical examination he had mild icterus, enlargement of the liver and spleen, fluid in the abdomen, prominent veins over the abdomen, hemorrhoids, varicosities and edema of the legs—all of which fit the diagnosis of portal cirrhosis. I cannot explain why he had such a low blood pressure. Undoubtedly he had a urinary infection. Evidence in the record indicates some degree of pyelonephritis. In addition, the abdominal pain, the anemia, the leukopenia, the reversed albumin-globulin ratio, the positive cephalin-flocculation test, the low cholesterol esters of 115 mg per 100 cc of a total of 241 mg, the bromsulfalein retention all speak for liver damage of the type one sees in portal cirrhosis. I assume that the fever was due to urinary infection, although fever is not uncommon in cirrhotic patients.

May we see the x-ray films?

DR JAMES J McCORT An examination of the gastrointestinal tract was made at the time of admission. The spot films of the esophagus show normal rugae without evidence of varices. The stomach shows no definite abnormality. There is a small diverticulum in the third portion of the duodenum. It is apparent that the spleen is enlarged and pressing on the stomach. There is also some enlargement of the left lobe of the liver as shown by the compression of the stomach.

The chest film taken on admission reveals clear lung fields. The heart is slightly prominent in the region of the left ventricle, there is no bulging anteriorly to indicate right-sided heart enlargement. It can be seen that the right leaf of the diaphragm is slightly higher than usual. A film of the chest at the time of the second admission, two months later, discloses an increase in vascular markings in both lung fields. The right leaf of the diaphragm is higher, and there is a small amount of fluid in the right costophrenic angle, posteriorly. A slight

under-aeration of the right lower lobe may be secondary to the high right leaf of the diaphragm.

DR LERMAN Can you judge whether or not the left lobe of the liver is the larger portion?

DR McCORT No, a film of the entire abdomen was not obtained.

DR LERMAN The subsequent rapid downhill course, in addition to the x-ray appearance of increased vascular congestion and the pulsating neck veins, again raises the question of congestive failure. It may be just incidental to the major problem. As I said before, all the facts so far seem to favor a diagnosis of ordinary portal cirrhosis.

We must consider other diagnoses such as syphilitic cirrhosis or gumma of the liver. The additional evidence that the left lobe of the liver was large is a characteristic finding in syphilitic cirrhosis. This is not sufficient evidence, however, to make the diagnosis, but it is suggestive. On the other hand, it is difficult to know whether syphilitic cirrhosis is different from ordinary portal cirrhosis. Many people believe that they are one and the same thing. Gumma is somewhat different. A gumma usually appears in the left lobe. It is the only suggestive bit of evidence. Hemochromatosis may be mentioned because he had pigmentation of the leg, but he did not have pigmentation elsewhere or evidence of diabetes. I assume that the pigmentation was due to stasis dermatitis associated with varicosities. Amyloid disease should be mentioned, even though there was no obvious cause for amyloidosis, other than possibly cirrhosis itself. The presence of a large liver and spleen and the albuminuria are consistent with a diagnosis of amyloidosis. Unfortunately, we have no other evidence, such as a Congo-red test. We can only mention it. Even primary amyloidosis might be a possibility.

Hepatoma should be mentioned, particularly in view of the rapid downhill course following the initial admission. The description of the liver is certainly not suggestive of hepatoma. Yet, in the presence of cirrhosis of long standing, rapid downhill course and weight loss, there is a good possibility that he had hepatoma. This produced sufficient obstruction to the biliary radicles to cause rapid liver failure.

We should also discuss the cause of death. Obviously he died from cholemia. What are the possibilities? I have already mentioned the co-existence of hepatoma. In addition, a patient with cirrhosis is rather subject to episodes of hepatitis or degeneration of the liver. I have seen several patients with portal cirrhosis who suddenly developed acute or subacute yellow atrophy or some sort of change in the cells that may be labeled hepatitis. The course here would suggest that he developed some such process as subacute yellow atrophy.

I must conclude with a diagnosis of portal cirrhosis, probably hepatoma, and probably a super-

imposed subacute degenerative process, such as subacute yellow atrophy

DR ALFRED KRAVES When Dr Lerman says "portal" does he mean of the so-called alcoholic type?

DR LERMAN Yes

DR KRAVES May not the previous history of jaundice have been a factor in the later development of cirrhosis? It is hard to tell from the history. One wonders if it was due to arsenic. Apparently he had syphilis twenty years previously and was treated with arsenic.

DR LERMAN One would expect the late damage from arsenic or hepatitis to develop within a few years, or there would be recurrent episodes of this damage as is so often observed following hepatitis — until it ends up in biliary cirrhosis.

CLINICAL DIAGNOSES

Cirrhosis of liver
Infectious hepatitis

DR LERMAN'S DIAGNOSES

Portal cirrhosis
Hepatoma — probable
Subacute yellow atrophy — probable

ANATOMICAL DIAGNOSES

Cirrhosis of liver portal
Hepatoma, with extension into vena cava and
right auricle of heart, and pulmonary metastases
Esophageal varices
Thrombosis of portal vein

PATHOLOGICAL DISCUSSION

DR MALLORY The exterior surface of the liver showed the coarse granularity characteristic of

a long-standing cirrhosis. The dome of the right lobe showed in addition a large nodule 6 cm in diameter that projected upward 2 to 3 cm from the surrounding tissue. When the liver was sectioned sagittally it was evident that the inferior vena cava was completely filled with a tumor thrombus that extended up into the right auricle of the heart. Tracing the tumor backward in sections of the liver, it was obvious that the hepatic veins were occluded, and there was a primary tumor in the liver substance occupying a considerable part of the right lobe. Histologically, it was a hepatoma, a primary liver-cell carcinoma, developing as it almost invariably does in a liver that has been cirrhotic for a long period. The cirrhosis itself was old and inactive. Beyond saying that it was a portal cirrhosis, I cannot classify it further. I cannot say whether or not it might have been a result of previous hepatitis or a result of alcoholism — greater than admitted. There was evidence of acute degeneration of liver cells in many parts of the organ itself, infarct-like in character and secondary to the numerous vascular occlusions. No distant metastases were found grossly, but in microscopical sections of the lung a very large proportion of the minute pulmonary arteries were solidly plugged with tumor thrombi, and quite probably in the terminal days or few weeks of life there was pulmonary hypertension and an element of cor pulmonale.

DR EDWARD B. BENEDICT How common are tumor thrombi with hepatoma?

DR MALLORY Four cases out of 5 invade the intrahepatic veins, usually the hepatic, sometimes the portal radicles. It is an exceptional case in which the tumor thrombus occludes the vena cava and grows into the right auricle, but we have seen it on several occasions. The one other tumor in which invasion of veins is equally extensive is hypernephroma, which can also grow up the vena cava and directly in the auricle.

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written by the disabled persons themselves, they are usually from the pens of laymen. The story of five years of compromise with a duodenal ulcer however is by a physician.²

This doctor, leading "a strenuous professional life that has yielded at least a modicum of success and perhaps even a little distinction," experienced his first attack of acute pain at the age of eighteen. From that time on his existence, far too familiar to many persons, was the usual one of repeated episodes of discomfort and pain, and of the conquest of discouragement.

This victim learned that the details of diet, alcohol, tobacco and exercise are personal ones, that the treatment must be the one best adapted to the needs and the temperament of the individual patient. He learned, as have many others, that bed is more valuable than diet, that rest and relaxation and an unfretted mind are more soothing than powders or drops of belladonna.

Ulcer, the "wound stripe of civilization," the torment of the ambitious and the penalty that the conscientious must too often pay, has become synonymous with the gnawing pain that robs one of his rest and removes the joy from living. Every ulcer casualty is the Spartan youth who kept the fox hidden beneath his cloak, even while it devoured his vitals. Nearly thirty-five years ago, intrepid Serbia, which would not let the captive Balkans sleep, became known as the "Serbian ulcer."

In general, as is known only too well in this country, "the sufferer from duodenal ulcer is characteristically of the type that will not compromise. Unless some catastrophe such as haemorrhage or perforation makes surrender incontestable, he will persist in the thick of the fight, even with one hand tied behind his back."

When his ulcer is not troubling him he cannot remember it, when its symptoms recur it will not let him forget its presence. Infrequently fatal, rarely completely incapacitating, the ubiquitous, unpredictable ulcer can hardly be classed among the dramatic calamities from which man's life and health may suffer. "And yet, it may be said that one's enjoyment of life is reduced by an ulcer to a greater extent than by some of the more serious disabilities" — except perhaps for those persons

who, regardless of their type, are able and willing to spend their lives in that compromise so distant from their natures.

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YOUNG MAN, GO WEST

EVEN free enterprise can learn a thing or two when it follows Horace Greeley's injunction to the Young Man. California Physicians' Service,—a Blue Shield Plan,—eager to help the visitor to California's shores, has inaugurated a courtesy travel service available to any of the physicians or lay people connected with any plan that is a member of the Associated Medical Care Plans.

In obtaining hotel rooms or travel reservations, giving advice on the best fishing grounds or tourist resorts, providing forwarding addresses, and even furnishing stenographic assistance, the two main offices as well as the fifteen district offices are at the visitor's service. This year and next are California's centennial years, during which a new pilgrimage of forty-niners is striking west. Members of Associated Medical Care Plans who are directing their steps toward the setting sun should jot the two addresses of Travel Department, California Physicians' Service, on their cuffs: 450 Mission Street, San Francisco 5, and 431 South Fairfax, Los Angeles 45.

Dr. Martin, of Hinsdale, N. H., was fined \$75 for violation of the liquor law in that State, by the Court of Common Pleas and yet he only sold it as a medicine, being himself a temperance man.

Boston M. & S. J., October 17, 1849

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

BACTERIOLOGIC SPECIMENS DELAYED IN THE MAIL

Physicians are advised that diagnostic specimens are not infrequently delayed in the mail, particularly if mailed near the end of the week. When important treatment is dependent upon an early report, it is wise, at least in the metropolitan area, where the distance is not too great, to send the specimen directly to the laboratory by special messenger.

Physicians are reminded that the diagnosis of diphtheria is a clinical and not a laboratory responsibility. Delay in the administration of antitoxin pending laboratory confirmation is very dangerous, and may result in a fatal outcome for the patient. Furthermore, a negative laboratory report does not exclude the diagnosis of clinical diphtheria, for the throat swab may not have reached the actual focus of the diphtheria organism. Since treatment for diphtheria may render a culture negative that would otherwise be positive, specimens should always be taken *before* treatment is begun.

MISCELLANY

STUART McGUIRE LECTURE SERIES AND SYMPOSIUM ON HEMATOLOGY

The twenty-first annual Stuart McGuire Lecture Series and Symposium on Hematology were held at the Medical College of Virginia in Richmond from September 28 to October 1. Sir Lionel E. H. Whitty, Regius Professor of Physics, Department of Medicine, Cambridge, England, delivered the lectures, entitled "The Physiology of Hemopoiesis," "Dyshemopoiesis from Nutritional and Specific Deficiencies," and "Dyshemopoiesis from Noxious Agents." New England was represented at the symposium by William P. Murphy, M.D., of Boston, who spoke on the subjects "The Treatment of Pernicious Anemia" and "Some Frequently Overlooked Sources of Anemia"; Louis K. Diamond, M.D., of Boston, who spoke on the subjects "The Anemias Resulting from Rh Incompatibility" and "Anemias of Childhood"; Thomas H. Ham, M.D., of Boston, who spoke on the subject "Acquired Hemolytic Anemia"; and F. H. L. Taylor, of Boston, who spoke on the subject "Recent Advances in Hemophilia."

NEW DIRECTOR OF RING SANATORIUM AND HOSPITAL

Dr. Benjamin Simon was recently appointed medical director of the Ring Sanatorium and Hospital in Arlington Heights, Massachusetts, succeeding Dr. Charles E. White. Dr. Simon, who received his degree from Washington University School of Medicine, was formerly assistant clinical professor of psychiatry and mental hygiene at Yale University School of Medicine and attending psychiatrist at the Veterans Administration Hospital in Newington, Connecticut, as well as acting assistant superintendent at Worcester State Hospital and clinical director of the Connecticut State Hospital. He is chairman of the New England Regional Survey Committee of the American Academy of Neurology.

BOOK REVIEW

Aesculapius Comes to the Colonies. The story of the early days of medicine in the thirteen original colonies. By Maurice B. Gordon, M.D. 8°, cloth, 560 pp., with 107 illustrations. Ventnor, New Jersey: Ventnor Publishers, Incorporated, 1949. \$10.00.

This history of early Colonial medicine in the United States is arranged by states, according to their dates of founding, beginning with Virginia and ending with Georgia, the last British colony to be founded. The work is a compilation from acknowledged sources which are listed by states in the final chapter. It is noted that certain important sources relating to medicine in Massachusetts have been omitted.

The material in Dr. Gordon's history is well arranged. There is a very good index. The publishing is excellent. A soft, light, nonglare paper is used, making the volume easy to handle. The illustrations on plate paper are tipped into the text. The volume should be in all medical and public libraries.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Blood Transfusion. By Elmer L. DeGowin, M.D., associate professor of internal medicine, State University of Iowa, College of Medicine, director, Blood Transfusion Service, University Hospitals, member of the Committee on Blood and Blood Derivatives, National Research Council, and member of the Advisory Board for Health Services, American National Red Cross, Robert C. Hardin, M.D., assistant professor of internal medicine, State University of Iowa, College of Medicine, and John B. Alsever, M.D., senior surgeon, United States Public Health Service, and chief, professional standards, Hospital Division, United States Public Health Service. 8°, cloth, 587 pp., with 200 illustrations. Philadelphia: W. B. Saunders Company, 1949. \$9.00.

In this new book the authors cover the entire field of blood transfusion, including whole blood, to which they have given over one hundred pages. The authors, internists, with an experience individually of ten years in the subject, believe "that whole blood transfusion is still, and will continue to be the major need in the treatment of patients." The early chapters are devoted to a short history, the clinical use of blood and its derivatives, immunology of blood and laboratory procedures. The remaining chapters discuss in detail the transfusion of whole blood, preparation and administration of plasma, and of the blood derivatives and plasma substitutes, and transfusion services and apparatus. Lists of references are appended to the various subdivisions of the text. There is a good index. The type and printing are excellent. The book should be in all medical libraries and in the collections of all surgeons.

Searchlights on Delinquency. New psychoanalytic studies. Dedicated to Professor August Aichhorn, on the occasion of his seventieth birthday, July 27, 1948. Managing editor K. R. Eissler, M.D., Ph.D., chairman of the editorial board, Paul Federn, M.D. 8°, cloth, 456 pp. New York: International Universities Press, Incorporated, 1949. \$10.00.

This memorial volume contains contributions by thirty-five authors, covering the whole field of juvenile delinquency. There is a short preface by Ernest Jones, a short biographic sketch of Professor Aichhorn, who was a friend and associate of Sigmund Freud and the author of *Wayward Youth*, and a bibliography of his writings. The work is divided into seven parts: general problems, clinical problems, technique and therapy, etiology and development, social psychology, penology, and surveys. There is a paper by Anna Freud entitled "Certain Types and Stages of Social Maladjustment." The book is well published, but the lack of an index mars its excellency. The volume should be in all collections on psychoanalysis and delinquency.

Studi e ricerche sulla manna e mannite naturale. By Domenico Gigante. 8°, paper, 144 pp. Rome: Istituto Poligrafico Dello Stato Libreria, 1948.

This monograph comprises a study of manna, the exudation of the manna ash tree or *Fraxinus ornus*, and mannite or mannitol, its principal constituent, a mild aperient and cholagogue. The study is thorough, considering the pharmacognosy of manna and its chemistry, the dosage of mannite, its method of extraction and preparation and its pharmacology, the action of manna and mannite on gastric function and on intestinal motility, on the liver and biliary tract, and their purgative and diuretic action, their therapeutic use in diseases of the respiratory organs and diabetes, and the use of mannite in functional and radiologic exploration of the biliary tract. Two appendixes consist of receipts for the medical use of manna and mannite and for the dietetic use of mannite in diabetes. A bibliography concludes the text.

Psychodynamics and the Allergic Patient By Harold A. Abramson, M.D., associate physician for allergy, The Mount Sinai Hospital, New York City, consulting physician for allergy, Sea View Hospital, Staten Island, New York, and assistant professor of physiology, Columbia University College of Physicians and Surgeons. 12°, cloth, 81 pp., with 7 illustrations. Saint Paul Bruce Publishing Company, 1948. \$2.50 (An official publication of the American College of Allergists.)

This special small volume comprises two short essays by Dr. Abramson entitled "Psychomatic Aspects of Hay Fever and Asthma Prior to 1900" and "Psychodynamics and the Allergic Patient," constituting in all thirty-six pages. Appended to the essays is the report of a panel discussion by ten well known authorities on allergy, comprising forty-five pages of text.

Atlas of Oral and Facial Lesions and Color Film Library By Ralph H. Brodsky, D.M.D., consulting oral surgeon, Department of Hospitals, New York City, lecturer in stomatology, New York University College of Medicine, associate dentist to the Mt. Sinai Hospital, New York, and founder and executive-secretary, Pan American Odontological Association. 8°, cloth, 127 pp., with 100 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$30.00.

This atlas, with its accompanying collection of one hundred colored slides, presents a new type of teaching unit for the dentist and oral surgeon. The slides depict lesions of the face and oral cavity. The text, supplied with the film slides, discusses the important features of the lesion, its diagnosis and treatment. Each slide is represented in the text by a diaphragmatic drawing. The slides are contained in a plastic case, bound to match the volume and designed to stand on a shelf with the book.

The Doctor Wears Three Faces By Mary Bard. 8°, cloth, 254 pp. Philadelphia: J. B. Lippincott Company, 1949. \$3.00.

This novel relates the experiences of a doctor's wife, covering all the phases of medical practice and ending with a trip to an American Medical Association convention. The story is well written and entertaining and represents the better type of medical fiction.

Introduction to Physiological and Pathological Chemistry With laboratory experiments By L. Earle Arnow, Ph.D., Ph.D., M.B., M.D., director of research, Medical Research Division, Sharp and Dohme, Incorporated, Glenolden, Pennsylvania. With an introduction by Katharine J. Densford, R.N., B.A., M.A., D.Sc., professor of nursing and director of the school of nursing, University of Minnesota, Minneapolis. Third edition. 8°, cloth, 595 pp., with 144 illustrations. St. Louis: C. V. Mosby Company, 1949. \$4.00.

This textbook was first published in 1939. The second edition was reprinted four times during 1943-1945, speaking well for the popularity of the book. It is written in a simple manner for students. The text is divided into three parts: introduction to chemical science, physiologic and pathological chemistry, and introduction to laboratory chemistry. An appendix includes tables of the international atomic weights (1947) and chemical components of human blood, and a long article of thirty-five pages on stain removal from fabrics, with home methods, reprinted from *Farmers' Bulletin*, No. 1474. There is a good index. The material is well arranged, and the book well printed. It should prove useful as a ready reference source for medical libraries.

Operative Surgery By Frederick C. Hill, M.S. (Surg.), M.D., associate professor of surgery, The Creighton University School of Medicine, Omaha, Nebraska. With a foreword by Charles W. Mayo, M.S. (Surg.), M.D., Section on Surgery, Mayo Clinic, Rochester, Minnesota. 8°, cloth, 698 pp., with 255 illustrations. New York: Oxford University Press, 1949. \$12.75 (Oxford Medical Publications).

The author presents a treatise of practically pure operative surgery with the objective of providing a single-volume work on general surgery, in which the gross appearance of surgical lesions is described, the proper treatment indicated and detailed description of operative procedures given. There are short chapters on preoperative and postoperative treatment. The classification used is the age-old type of head to

foot. The author suggests operations he considers most suitable for the various surgical conditions described. The material is well arranged, and the text well written. The book is a personal one based on the author's experience and is not overloaded with redundant references to the surgical literature. It should prove interesting to all surgeons.

An Introduction to Cardiology By Geoffrey Bourne, M.D., F.R.C.P., physician, and physician in charge of the Cardiological Department, St. Bartholomew's Hospital. 8°, cloth, 264 pp., with 65 illustrations. Baltimore: Williams and Wilkins Company, 1949. \$4.50.

This small manual, which endeavors to portray the chief aspects of cardiovascular disease, is based largely on lectures given at St. Bartholomew's Hospital, London, and on the author's personal experience. The material is well arranged, condensed and written. This is a personal book, and references to the literature are omitted from the text. In the introduction the author refers to three standard works that he recommends for collateral reading, among which he mentions *Heart Disease*, by Dr. Paul D. White, of Boston, as being the best detailed textbook on the subject. The book is well published. The printing was done in Great Britain.

Thank God for My Heart Attack By Charles Y. Harrison. 12°, cloth, 144 pp. New York: Henry Holt and Company, 1949. \$2.50.

This popular book, although it may be classed as non-fiction, has all the aspects of a novel. Mr. Harrison, a well known writer, suffered an attack of coronary thrombosis, from which he recovered. In this book he relates his experiences while he was ill and until the time he returned to his work of writing. The text is well written and interesting.

NOTICES

ANNOUNCEMENTS

Dr. Joseph Bernard Doyle announces the removal of his office for the practice of gynecology and obstetrics to 65 Bay State Road, Boston.

Dr. John J. Finn, Jr., announces the opening of an office at 270 Commonwealth Avenue, Boston, for the practice of internal medicine.

Dr. Milton H. Rodofsky announces the removal of his office to 478 Beacon Street, Boston.

Dr. Arthur A. Wills, Jr., has resigned his position as assistant medical director with the Travelers Insurance Company, Hartford, Connecticut, and plans to resume the practice of medicine at 815 Sheraton Building, 10 Post Office Square, Boston.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A regular meeting of The New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, Boston, on Tuesday, November 8, at 8:00 p.m. The subject "Decamethonium Iodide. Its Uses in Conjunction with Pentothal Sodium and Nitrous Oxide Oxygen in Abdominal Surgery" by Drs. Francis F. Foldes and Theodore S. Machaj, of the Department of Anesthesia, Mercy Hospital, Pittsburgh, Pennsylvania, will be presented by Dr. Francis F. Foldes.

AMERICAN INSTITUTE OF ARCHITECTS

The six New England chapters of the American Institute of Architects will hold a seminar on hospital design at the Hotel Kenmore, Boston, on December 1 and 2. Leaders in the hospital field will discuss the solution of problems encountered in the design of hospitals of small and medium size. The program will include topics of interest to hospital consultants and administrators and medical personnel, as well as professional architects.

(Notices concluded on page 20)

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VARIATIONS IN THE FIRST APICAL SOUND SIMULATING THE SO-CALLED "PRESYSTOLIC MURMUR OF MITRAL STENOSIS"*

A Phonocardiographic Study

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MANILA, PHILIPPINE ISLANDS, AND BOSTON, MASSACHUSETTS

ALTHOUGH Fauvel,¹ in 1843, attributed the apical presystolic murmur to stenosis of the mitral valve, Duroziez's² description — "flout-tata-rou"— in 1862 has been considered as the classic auscultatory sign. Since then, numerous observations and studies have confirmed the original concepts, and modifications have been added.

A few additional observations are herewith reported, with particular reference to the so-called "presystolic crescendo murmur." We have observed by means of the phonocardiographic technic that auscultatory presystolic murmurs may at times be an auscultatory illusion owing to certain variations in the first heart sound. Although our series is small, we consider these observations pertinent to an accurate clinical evaluation of this physical finding.

PREVIOUS STUDIES

A presystolic murmur at the apex is generally regarded as evidence of mitral stenosis. It has been considered as a pathognomonic sign of such valvular disease, either when found alone or in association with a mid-diastolic rumble.³ Some observers⁴ believe that in lesser degrees of mitral stenosis, the presystolic murmur may actually be an earlier sign than the mid-diastolic murmur. On the other hand, Bland, White and Jones^{5, 6} suggested that a mid-diastolic murmur does not necessarily indicate organic mitral stenosis. They noted that the mid-diastolic murmur disappeared as cardiac size returned to normal and attributed this murmur to dilatation of the left ventricle.

The presystolic murmur is commonly described as having a rapidly increasing intensity, with a

so-called crescendo effect. It is associated with auricular systole, which increases the velocity of blood flow through the stenosed mitral opening, whereas the mid-diastolic murmur generally begins with the opening of the mitral valve (fourth component of the second sound).⁷

Phonocardiography has shown that the crescendo character of the presystolic murmur is an inconstant phenomenon, as reported by Johnston⁸ and Battro and Braun-Menendez.⁹ Quite often, the mid-diastolic murmur is registered with a diminishing character, actually disappearing just prior to the first heart sound. In fact, the presystolic murmur may not be audible in all cases of mitral stenosis, especially when the auricular contraction is feeble. The reason for this effect is that the velocity of blood flow through the stenosed mitral valve is greatly diminished, and the resultant pitch of the murmur falls below the threshold of audibility. Reid,¹⁰ in a survey of autopsy findings at the Boston City Hospital in 1921, found 8 cases of mitral stenosis in which a presystolic murmur had not been heard during life, whereas 2 other patients exhibited a presystolic murmur but failed to show any organic lesion in the mitral valve. In 1895 Phear¹¹ described 46 cases with presystolic murmur in which no mitral lesion was found at post-mortem examination. They were aortic regurgitation in 17, adherent pericarditis in 20 and dilated heart in 9.

A more controversial point is the cause of the presystolic murmur. Mackenzie¹² was the first to notice its disappearance in auricular fibrillation. From this observation, and from its relation to both the "a" wave of the jugular phlebogram and the "P" wave of the electrocardiogram, it was concluded that auricular contraction was the cause. However, the fact that its crescendo character is inconstant and that crescendo murmurs have also been observed in auricular fibrillation itself has led others even to doubt the role of auricular contraction in its production.¹³⁻¹⁵ Reid,¹⁶ in 1921,

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‡Department head, Electrophysiological Research, Sanborn Company, Cambridge, Massachusetts.

§Chief of staff, House of the Good Samaritan; associate physician, Massachusetts General Hospital.

described a modification of the first sound that he believed to be due to an early systolic murmur that gave the impression of a presystolic murmur ending in a sharp first sound. Cossio and Berconsky¹⁷ noted on the phonocardiogram either an early systolic murmur initiating the first-sound complex or a low coarse wave. They interpreted the latter, in mitral stenosis, as due to the precordial impact of the cardiac apex during the initial phase of ventric-

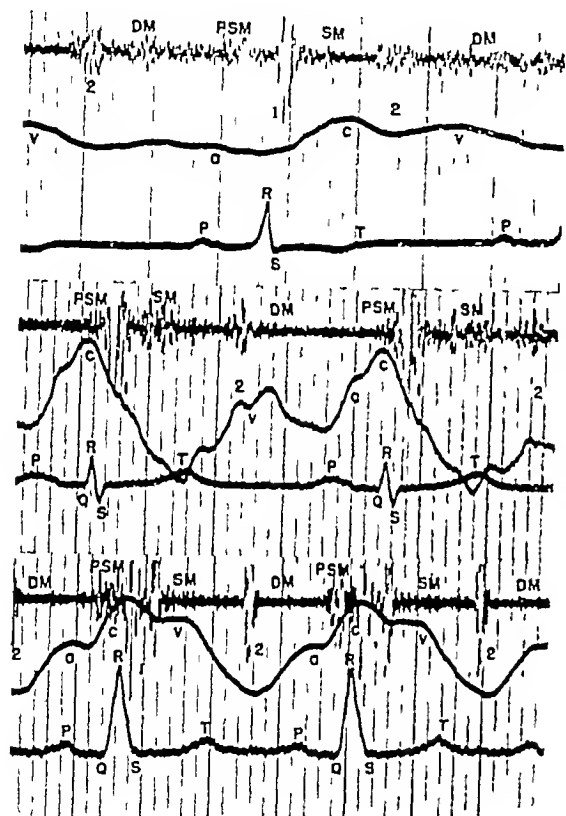


FIGURE 1 Presystolic Murmur in Mitral Stenosis

Phonocardiograms taken over the apex in 3 cases of mitral stenosis and insufficiency, show the systolic, mid-diastolic and presystolic murmurs. The last starts definitely before the electrocardiographic Q wave. The presystolic murmur shows no crescendo character in the upper tracing, slight crescendo in the middle tracing and more definite crescendo in the lower tracing. In all cases the first sound itself is markedly accentuated.

11

murmur, all the patients having normal hearts at autopsy. Bramwell and Ellis²⁰ examined 192 athletes at the Amsterdam Olympics in 1931 and discovered in 12 long-distance runners a first sound indistinguishable from a presystolic murmur and accentuated first sound.

According to White,²¹ "marked accentuation and slurring of the first sound, such as not infrequently occurs in an overactive heart may give a semblance of a slight presystolic murmur and cause an erroneous diagnosis of mitral stenosis to be made when excitement, exertion, some nervous factor as neurocirculatory asthenia, or thyrotoxicosis, is responsible." Furthermore, he regards the auditory illusion of a crescendo character of the presystolic accentuation of the mitral diastolic murmur as "due to the combined presence of a sudden accentuation of a murmur that has largely died away and the sharp first heart sound that terminates it." This is illustrated in Figure 1.

Reid²² tried to classify presystolic murmurs into two types: the true and the false. The first type, he states, is the one that has always been interpreted as due to auricular systole in mitral stenosis. It is low pitched, not definitely crescendo, and is simply an accentuation of an earlier diastolic murmur. On the other hand, the false type is usually a crescendo murmur of early ventricular systole. This is the one more frequently noted, since it may be heard both in cases of mitral stenosis and in normal hearts. It is loud, rough and out of proportion to the strength of auricular systole and presents no gap before the first sound.

In addition, a variety of auscultatory phenomena may exist whose unusual combinations may give rise to an acoustic impression of a presystolic crescendo murmur, such as those described by Taquini, Massell and Walsh²³ and by Luisada and Montes.²⁴

PRESENT STUDIES

The present series consists of 8 patients, all of whom were thought to have a presystolic apical murmur, and yet phonocardiography failed to corroborate this auscultatory interpretation. Instead, certain variations of the first sound were noted, which could well explain the auscultatory error. In most of these cases, the murmur was clinically described as definitely crescendo. As a result, in 7 patients with a positive or probable history of rheumatic fever the diagnosis of mitral stenosis was either considered or actually made, particularly when this murmur was associated with an earlier diastolic component. In the sole non-rheumatic case, the presystolic murmur was interpreted as an Austin-Flint murmur in aortic insufficiency of syphilitic nature.

The cases may be divided into three groups, based on their final clinical diagnoses. The first group (Case 1, 2 and 3) consisted of patients who definitely

ular systole, in view of the delayed closure of the auriculoventricular valves. Furthermore, several observers detected identical auscultatory findings in persons with normal hearts. In 1909 Sewall¹⁸ stated that "in the structurally normal heart, especially in conditions of circulation excitement, the first sound frequently begins with crescendo tone, simulating closely the faint and brief presystolic murmur or acute accent initiating the first sound in mitral stenosis." Irons and Jennings¹⁹ reported 4 cases in which a clinical diagnosis of mitral stenosis was made because of a presystolic

had valvular disease. Two had rheumatic heart disease with predominant aortic regurgitation and mitral regurgitation, the other was a case of syphilitic aortitis with aortic insufficiency. In the 2 rheumatic cases the associated apical diastolic murmur with what was believed to be a presystolic crescendo led to the additional diagnosis of mitral stenosis. Without a presystolic element, the diastolic murmur itself would not have suggested mitral stenosis in view of the possibility of its being an Austin-Flint murmur. On the other hand in the third case a suspected Austin-Flint murmur

because of a presystolic murmur that was believed to be present. No mid-diastolic murmur was heard. The phonocardiograms, however, disclosed no presystolic murmur. The cardiac status in both cases was then declared normal.

The phonocardiograms were taken with the Sanborn Tribeam Phonocardiograph both the stethoscopic and the logarithmic microphones and the large open-bell chest piece being used. The subjects were examined in the supine position and the phonocardiograms taken while the breath was held in mid-expiration. For reference tracings

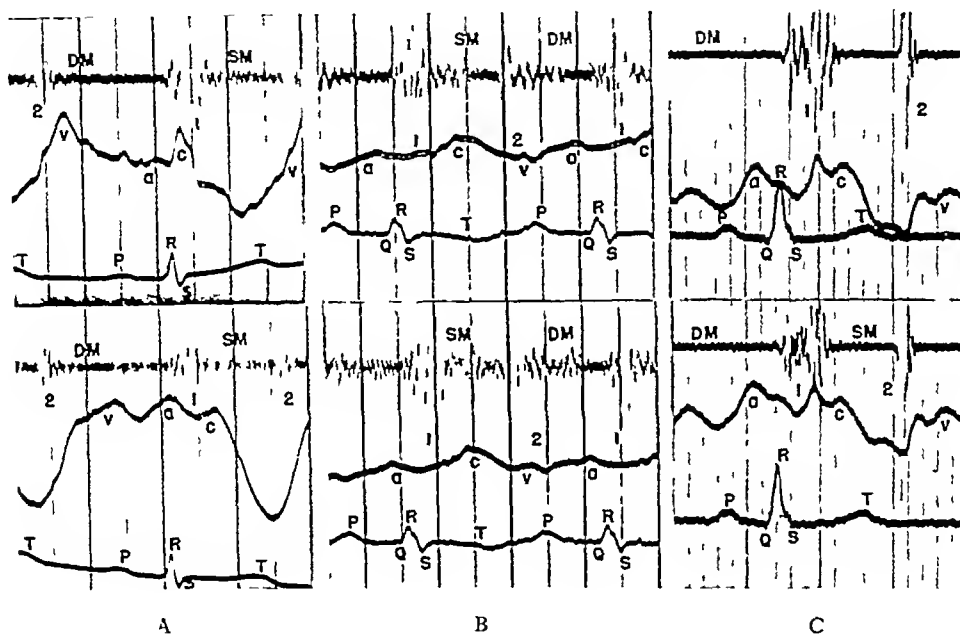


FIGURE 2 Cases of Valvular Heart Disease

Stethoscopic (upper) and logarithmic (lower) phonocardiograms taken at the apex, with simultaneous recording of the jugular phlebogram and Lead 2 electrocardiogram. In A (Case 1), B (Case 2) and C (Case 3) there are systolic and diastolic murmurs but no presystolic crescendo murmur. Instead, the first sound has a crescendo configuration. In addition, a systolic gallop is present in B (Case 2), and a wide splitting of the first sound in C (Case 3).

failed to be confirmed by subsequent phonocardiograms.

The second group (Case 4, 5 and 6) comprised patients with congenital cardiovascular anomalies: coarctation of the aorta in 1, subaortic stenosis in another, and an undetermined anomaly as an element of Marfan's syndrome in the third. In addition, they were all thought to have associated rheumatic mitral stenosis because of the presence of an apical diastolic murmur with the so-called presystolic crescendo. It is interesting to note that the post-mortem findings in the last case showed no valvular lesion at all; instead, an aneurysm of the ascending aorta was discovered.

The third group (Case 7 and 8) illustrates cases in which a diagnosis of mitral stenosis was made

electrocardiographic Lead 2 and either the right jugular phlebogram or the apex cardiogram were registered simultaneously with the phonocardiogram.

It can thus be seen that three types of phonocardiographic registration have been employed in this study — namely, linear stethoscopic and logarithmic.⁷⁻²⁵ The linear phonocardiogram or apex cardiogram represents graphically the mechanical vibrations set up by cardiac action as they exist on the surface of the patient's chest. The stethoscopic phonocardiogram registers the cardiac sound vibrations as they are presented to the ears of an observer by an average acoustic stethoscope. Finally, the logarithmic phonocardiogram is the graphic registration of the cardiac sound vibrations

as they are perceived by the average observer of normal hearing when an average acoustic stethoscope is employed. These phonocardiographic techniques enable one to register and analyze all existing cardiac sound vibrations of both low and high frequency. Logarithmic phonocardiography, however, is the actual representation of what should be perceived on clinical auscultation.

CASE REPORTS

CASE 1 J D, a 14-year-old boy, had a clinical diagnosis of rheumatic heart disease, aortic regurgitation, mitral regurgitation, and probable mitral stenosis. At the age of 4 years, he had his initial attack of rheumatic fever with polyarthritis. This recurred a year and a half prior to the

the cause of the auscultatory illusion of a presystolic crescendo murmur.

CASE 2 C K, a 16-year-old girl, had rheumatic heart disease, aortic and mitral regurgitation and probable mitral stenosis. In addition, a suspicion of an auricular septal defect was considered because of a Grade II to III systolic murmur over the pulmonic area. Her first rheumatic-fever episode had occurred at the age of 8 years. On physical examination, she was found to be underweight and underdeveloped. There was a noticeable bulging of the left precordium. The heart was enlarged to the left. No thrill was felt. At the apex, a Grade II systolic murmur and a Grade I presystolic murmur were described. Likewise, a Grade II aortic diastolic murmur was noted along the left sternal border. X-ray examination revealed a moderately enlarged heart, particularly the right ventricle, with a somewhat dilated pulmonary artery.

The phonocardiograms (Fig 2B) disclosed both systolic and diastolic murmurs over all auscultatory areas, and a

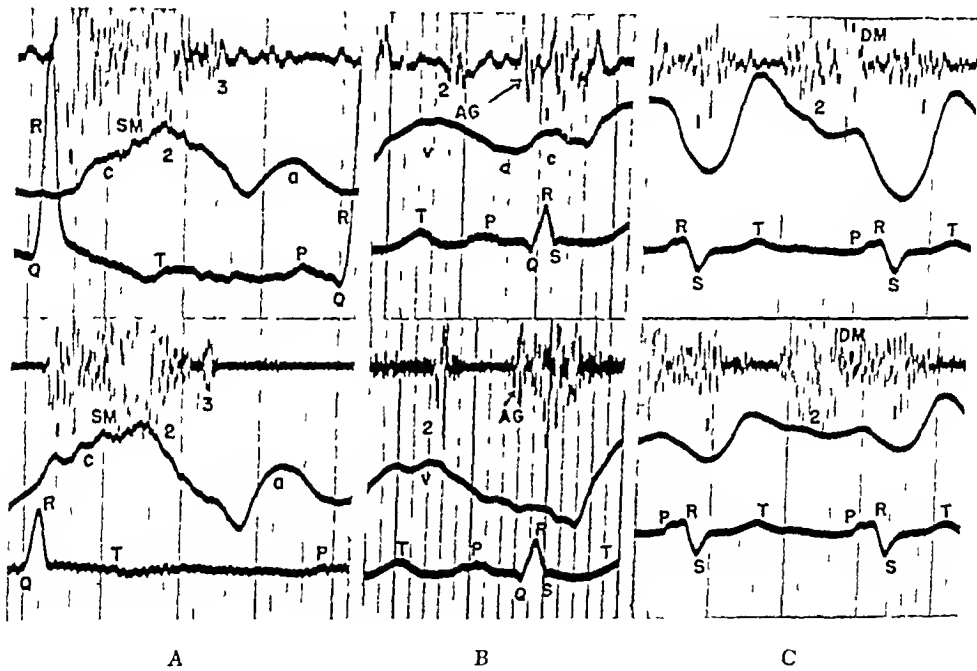


FIGURE 3 Congenital Cases

These are simultaneously recorded stethoscopic (upper) and logarithmic (lower) phonocardiograms with jugular phlebograms and Lead 2 electrocardiograms. In A (Case 4) note the crescendo configuration and splitting of the first sound, better shown in the logarithmic tracing, also, a definite third sound is registered. In B (Case 5) an auricular gallop (AG) closely precedes the first sound, which is prolonged and with an early crescendo configuration. In C (Case 6) the first sound is crescendo in configuration, the split second sound is well shown in the logarithmic tracing.

present admission. He had never had any congestive failure. Physical examination revealed a slightly enlarged heart, with a rate of 80 per minute and a blood pressure of 105/65. No thrill was felt. At the apex, the first sound was masked by a Grade III systolic murmur. A long diastolic rumble with presystolic crescendo was described. There was also a Grade II aortic diastolic murmur.

The phonocardiograms (Fig 2A) at the apex showed a prominent systolic murmur, and a murmur throughout diastole but without any presystolic crescendo. The diastolic murmur was more distinctly registered logarithmically than stethoscopically. However, the first sound had a crescendo configuration, clearly shown in both the stethoscopic and the logarithmic phonocardiograms. The first sound definitely began after the electrocardiographic Q wave, as is normal for the first sound, a presystolic murmur precedes the Q wave. This variation in the first sound must have been

systolic apical gallop. No presystolic crescendo was shown. The first sound assumed a crescendo configuration, starting after the electrocardiographic Q wave. Further investigations showed that the apical diastolic murmur was transmitted from the aortic region. Thus, the diagnosis of mitral stenosis was seriously doubted.

CASE 3 C S, a 43-year-old man, had syphilitic heart disease with aortic insufficiency. There was no history of rheumatic fever. On physical examination, the heart was borderline in size by percussion. The second aortic sound was more intense than the second pulmonic sound. Along the third and fourth left interspaces close to the sternal border, a Grade I early diastolic murmur was heard. Over the apex, although no definite mid-diastolic murmur was noted, a presystolic crescendo murmur was described. The blood pressure was 140/70.

The phonocardiograms at the apex (Fig 2C) disclosed no presystolic murmur at all. Instead, the first sound was widely split, with a typical crescendo configuration of its component elements beginning after the electrocardiographic Q wave.

CASE 4 S K, a 22-year-old man, had a diagnosis of probable congenital subaortic stenosis, in view of an aortic thrill and a harsh aortic systolic murmur dating back to an early age. On physical examination, the heart was found to be only slightly enlarged. At the apex, two extra sounds or short murmurs were described in diastole—one protodiastolic, and the other presystolic. A question of rheumatic heart disease was thus considered, with probable mitral-valve involvement.

Phonocardiograms (Fig 3d) revealed that the protodiastolic element was actually a third sound, whereas the presystolic element was in reality part of the first heart sound. Because the first sound was split, with its latter element of

heard in all areas. Over the base, a high-pitched diastolic murmur was also noted. The congenital cardiac anomaly was not defined during life. However, associated rheumatic disease of the mitral valve was suspected, in view of the apical findings on auscultation. The patient later went into uncontrollable congestive failure. Subsequent post-mortem examination failed to show any mitral lesion, and the only cardiovascular findings were a markedly hypertrophied and dilated heart, and an aneurysm of the ascending aorta.

The phonocardiograms in this case (Fig 3C) revealed that although there was a diastolic apical murmur, it was actually diminuendo in character. However, the first sound itself had a crescendo configuration, explaining the crescendo effect on auscultation.

CASE 7 J C, a 16-year-old boy, was thought to have mitral stenosis because of an accentuated first apical sound and a presystolic murmur, in addition to a so-called "mitral-shaped heart" on x-ray study. However, no left auricular

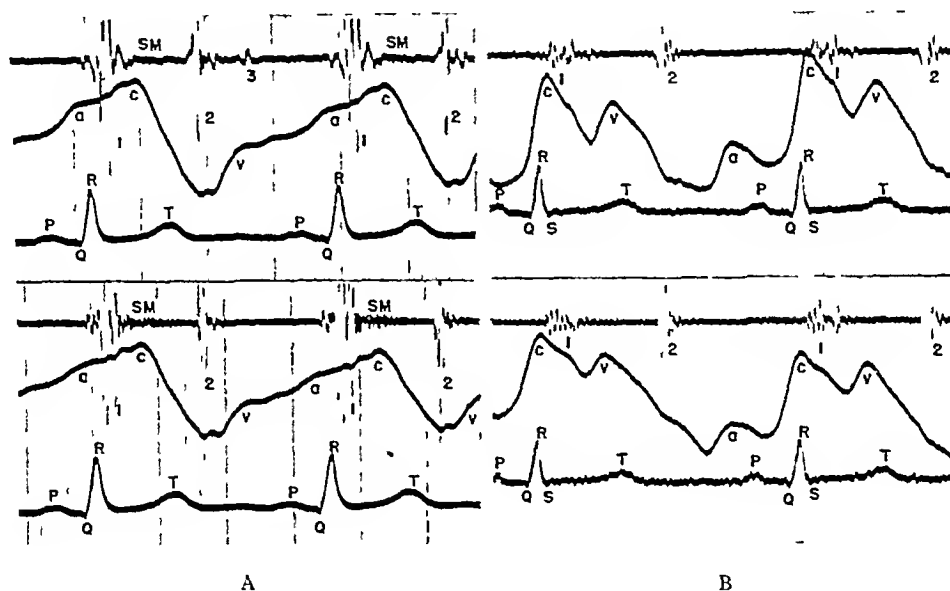


FIGURE 4 Normal Cases

These are simultaneous phonocardiograms, phlebograms and Lead 2 electrocardiograms. The upper phonocardiograms are stethoscopic, and the lower ones are logarithmic. In A (Case 7), as well as in B (Case 8), the first sound has a crescendo configuration. In addition, it is split and prolonged in B (Case 8).

greater intensity than the earlier one, an auscultatory illusion of a presystolic crescendo murmur was produced. This is better illustrated in the logarithmic phonocardiogram, which represents what was actually heard.

CASE 5 V K, a 47-year-old woman, had coarctation of the aorta. She also had rheumatic heart disease mainly aortic regurgitation. An additional diagnosis of mitral stenosis was considered because of an accentuated first apical sound and a presystolic murmur. X-ray examination showed a slightly enlarged heart, with slight notching of the ribs.

Phonocardiography (Fig 3B) revealed an auricular gallop followed by a prolonged first sound. In view of the close proximity of the auricular gallop to the first sound and the prolongation of the latter, an auscultatory illusion of a presystolic murmur was produced. Again the logarithmic phonocardiogram showed a crescendo configuration of the first sound.

CASE 6 V B, a 25-year-old woman had Marfan's syndrome with arachnodactyly, bilateral dislocation of the lenses oculi and various heart findings. The heart was markedly enlarged, with a heaving impulse that shook both the patient and the bed. At the apex a diastolic thrill was felt and a Grade III to IV diastolic murmur with a presystolic crescendo was described. A systolic murmur of minimal intensity was

enlargement was reported. On the other hand, bilateral pleural effusion and pericardial fluid were noted. Systolic murmurs at both apex and base were also described.

Phonocardiograms (Fig 4d) disclosed no presystolic murmur at all. The first sound itself, however, had a crescendo configuration.

CASE 8 E M, a 34-year-old woman, had a diagnosis of probable rheumatic heart disease with slight mitral stenosis. Two of her children had rheumatic fever. On physical examination she was pale and thin. Her heart was not enlarged. Auscultation revealed what was described as a short presystolic murmur. In view of this finding, her complaints of hemoptysis and slight elevation of temperature were considered as possible manifestations of low-grade rheumatic-fever activity.

However, the phonocardiograms (Fig 4B) clearly showed no presystolic murmur at all. Instead, the first apical sound was split and prolonged, the later elements of the split sound being of greater intensity than the earlier ones. In the absence of any definite presystolic murmur, the diagnosis of mitral stenosis was abandoned. The whole clinical picture was then attributed to pulmonary tuberculosis, which was further substantiated by the fact that the fever was typically nocturnal and that her husband was tuberculous.

as they are perceived by the average observer of normal hearing when an average acoustic stethoscope is employed. These phonocardiographic techniques enable one to register and analyze all existing cardiac sound vibrations of both low and high frequency. Logarithmic phonocardiography, however, is the actual representation of what should be perceived on clinical auscultation.

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CASE 1 J D, a 14-year-old boy, had a clinical diagnosis of rheumatic heart disease, aortic regurgitation, mitral regurgitation, and probable mitral stenosis. At the age of 4 years, he had his initial attack of rheumatic fever with polyarthritides. This recurred a year and a half prior to the

the cause of the auscultatory illusion of a presystolic crescendo murmur.

CASE 2 C K, a 16-year-old girl, had rheumatic heart disease, aortic and mitral regurgitation and probable mitral stenosis. In addition, a suspicion of an auricular septal defect was considered because of a Grade II to III systolic murmur over the pulmonic area. Her first rheumatic-fever episode had occurred at the age of 8 years. On physical examination, she was found to be underweight and underdeveloped. There was a noticeable bulging of the left precordium. The heart was enlarged to the left. No thrill was felt. At the apex, a Grade II systolic murmur and a Grade I presystolic murmur were described. Likewise, a Grade II aortic diastolic murmur was noted along the left sternal border. X-ray examination revealed a moderately enlarged heart, particularly the right ventricle with a somewhat dilated pulmonary artery.

The phonocardiograms (Fig 2B) disclosed both systolic and diastolic murmurs over all auscultatory areas, and a

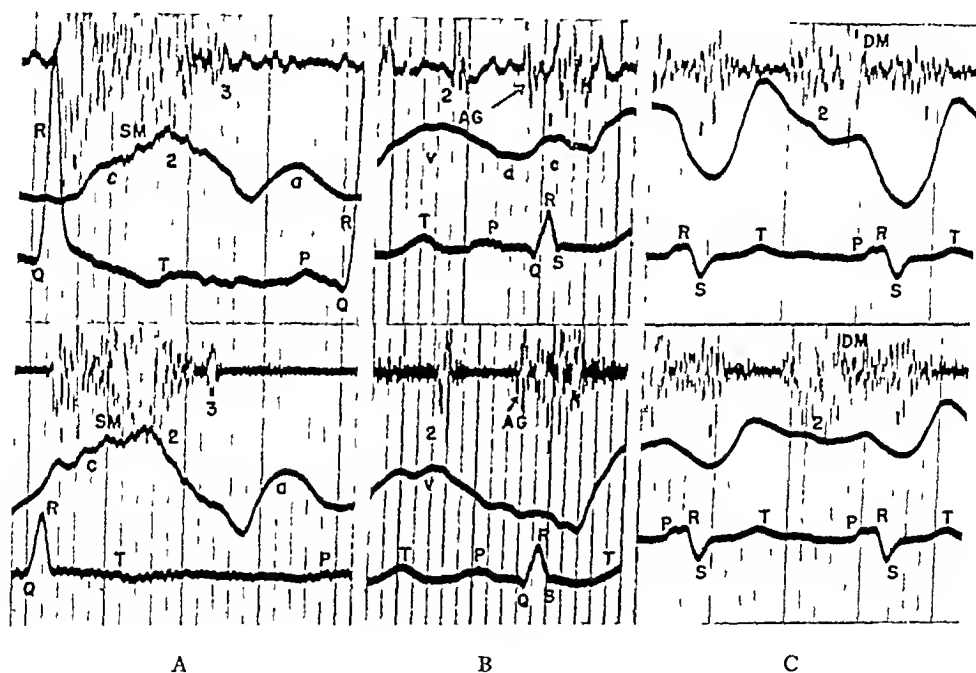


FIGURE 3 Congenital Cases

These are simultaneously recorded stethoscopic (upper) and logarithmic (lower) phonocardiograms with jugular phlebograms and Lead 2 electrocardiograms. In A (Case 4) note the crescendo configuration and splitting of the first sound, better shown in the logarithmic tracing, also, a definite third sound is registered. In B (Case 5) an auricular gallop (AG) closely precedes the first sound, which is prolonged and with an early crescendo configuration. In C (Case 6) the first sound is crescendo in configuration, the split second sound is well shown in the logarithmic tracing.

present admission. He had never had any congestive failure. Physical examination revealed a slightly enlarged heart, with a rate of 80 per minute and a blood pressure of 105/65. No thrill was felt. At the apex, the first sound was masked by a Grade III systolic murmur. A long diastolic rumble with presystolic crescendo was described. There was also a Grade II aortic diastolic murmur.

The phonocardiograms (Fig 2A) at the apex showed a prominent systolic murmur, and a murmur throughout diastole but without any presystolic crescendo. The diastolic murmur was more distinctly registered logarithmically than stethoscopically. However, the first sound had a crescendo configuration, clearly shown in both the stethoscopic and the logarithmic phonocardiograms. The first sound definitely began after the electrocardiographic Q wave, as is normal for the first sound, a presystolic murmur precedes the Q wave. This variation in the first sound must have been

systolic apical gallop. No presystolic crescendo was shown. The first sound assumed a crescendo configuration, starting after the electrocardiographic Q wave. Further investigations showed that the apical diastolic murmur was transmitted from the aortic region. Thus, the diagnosis of mitral stenosis was seriously doubted.

CASE 3 C S, a 43-year-old man, had syphilitic heart disease with aortic insufficiency. There was no history of rheumatic fever. On physical examination, the heart was borderline in size by percussion. The second aortic sound was more intense than the second pulmonic sound. Along the third and fourth left interspaces close to the sternal border, a Grade I early diastolic murmur was heard. Over the apex, although no definite mid-diastolic murmur was noted, a presystolic crescendo murmur was described. The blood pressure was 140/70.

UNSUSPECTED TRAUMA TO THE HEART DURING INTRATHORACIC SURGERY*

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IN RECENT decades, cardiac wounds have been carefully studied both in the laboratory^{1,3} and at the bedside.^{4,8} An entity has evolved in which we wish to stimulate new interest by a report of 2 cases of inadvertent damage to the heart during surgical procedures on other thoracic viscera. In each case the injury was fatal, but the signs of cardiac contusion went unidentified. In view of the increasing number of intrathoracic operations being performed, these examples of accidental trauma to the heart merit attention. We are unaware of a description of similar cases, but suspect that less disastrous wounds account for some of the cardiac arrhythmias reported after pneumonectomy and lobectomy.^{9,11}

CASE REPORTS

CASE 1 (L. H. H. 116985) § A 63-year-old man had a diffusely infiltrating carcinoma of the stomach without demonstrable metastases. The only abnormality of the cardiovascular apparatus was moderate arteriosclerosis of the peripheral arteries. A general anesthetic was administered on January 20, 1947, and a total gastrectomy was performed through a thoracoabdominal incision. Throughout the procedure, the patient was turned on the right side and inclined about 15° posteriorly from the lateral position.

The technic of resection was that of postcolic anastomosis. There was difficulty in suturing the esophagus to the jejunum, and to provide adequate exposure of the tissues, the diaphragm was retracted vigorously. At some time during the application of this force, there was an abrupt onset of tachycardia, the heart rate rising from 80 to 120 per minute. Except for this transient disturbance, the patient's operative course was uneventful. During resection, a liter of whole blood and an equal amount of physiologic saline solution were administered intravenously.

When returned to the ward, the patient was in good condition, but within 4 hours he developed the signs of circulatory collapse: the blood pressure fell from the normal level of 120/80 to 70/56, and the heart rate rose to 130 per minute. The reason for shock was obscure, physical examination providing no clues and nothing remarkable being revealed by a radiogram of the chest taken in the upright position. The patient rallied when given a transfusion of 500 cc of whole blood, but throughout the 1st postoperative night, he was apprehensive and complained of breathlessness and a sensation of pressure on the chest. He was provided with an oxygen tent and sedated with morphine.

On the following morning, he described severe substernal pain, and for the first time, an irregularity of the pulse was noted. The blood pressure was 100/70, the heart rate 100, and the respiratory rate 26. Throughout the ensuing day, the patient's condition remained precarious, but no change in the physical findings was detected.

Despite a transient return of blood pressure to normal on the 2nd postoperative morning, the patient's condition soon deteriorated, and shock supervened. The pulse continued to be irregular, but the type of arrhythmia was never determined since an electrocardiogram was not taken. Apprehension increased, and the temperature rose to 103.6°F,

the respiratory rate to 44, and the heart rate to 120. Coma ensued, and death occurred 53 hours after resection.

At autopsy (L. H. H. 3922) the pericardial sac was distended by several hundred cubic centimeters of partially clotted blood. The site of hemorrhage was an injured coronary vein close to the cardiac apex and on the anterior aspect of the left ventricle. Incision of the subjacent myocardium disclosed a superficial and poorly delineated purplish-red focus measuring 4 mm in depth and up to 15 mm in diameter. The cardiac muscle elsewhere was a uniform reddish brown. There was minimal arteriosclerosis of the coronary arteries. The heart weighed 390 gm.

Microscopical sections revealed a contusion limited to the outer third of the left ventricular wall. Where the coronary vein was involved in the injury, its smooth-muscle fibers were necrotic and separated by erythrocytes and polymorphonuclear leukocytes. In the underlying myocardium, there were degenerative changes in many of the muscle fibers, and between these damaged cells were polymorphonuclear leukocytes, extravasated red blood cells and a few lymphocytes. In the deeper portions of the lesion, the small blood vessels were engorged, and there were foci of extensive interstitial hemorrhage. Sections of heart muscle from other regions showed preservation of normal architecture.

The intestinal anastomoses were intact, and all portions of the bowel appeared to have been viable.

Tumor metastases were found in the regional lymph nodes and deep within the substance of the liver.

There were no other significant findings.

The heart was probably injured during anastomosis of the esophagus and jejunum. The patient's position on the table exposed the anterior aspect of the left ventricle to the retracting force used during that phase of the operation. The postoperative course was puzzling, but since no manipulation of the heart was recalled, hemopericardium did not seem likely. In retrospect, the evidence for that diagnosis was either misinterpreted or went unnoticed. Prior to circulatory collapse, there was no reason to listen for a pericardial rub, and subsequently, the quality of the heart sounds was readily attributed to the precarious state of the patient's circulation. Although taken only an hour after onset of shock, the normal radiogram of the heart was regarded as proof that effusion was not present. It has been taught, however, that the parietal pericardium stretches slowly, and when an effusion forms rapidly, the heart may be compressed before enough fluid has accumulated to be demonstrable roentgenographically.^{12,13} It is reasonable to invoke this concept to explain the postoperative collapse. As the parietal membrane was stretched, the patient's distress was relieved, but when further bleeding occurred, the signs of tamponade returned. Although trauma to cardiac muscle may cause a fall in blood pressure,^{3,14} myocardial damage was of secondary importance in this case.

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SUMMARY AND CONCLUSIONS

Eight cases in which a presystolic murmur was considered present by clinical auscultation but was not confirmed by phonocardiographic technic are presented

This auditory illusion was due to several forms of variation of the first heart sound, in all of which the whole sound complex assumed a crescendo configuration. These variations consisted in prolongation of the sound with its later elements of unusual intensity, splitting of the sound in such a fashion that the second element was more intense than the first and prolongation of the sound associated with an auricular gallop coming very close to the first sound. In all these variations, however, the first sound always started after the electrocardiographic Q wave.

Knowledge of such cardiac sound variations is important when one considers that they may produce an auditory illusion leading to serious diagnostic error in that the so-called presystolic crescendo murmur at the apex is indicative of organic mitral stenosis. Our clinical cases definitely show that such an error has been made.

It is for this reason that caution in the interpretation of this physical finding is emphasized, particularly in the uncharacteristic cases in which the murmur may be rather short and faint and in which there are no other convincing evidences of mitral stenosis. In such cases a careful phonocardiographic study is most helpful for a correct clinical diagnosis.

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ordinarily associated with coronary occlusion. Signs of congestive failure may evolve insidiously,^{14, 20} but in some cases pulmonary edema has a rapid onset.²¹ The weakness of the heart is usually transient, but the patient's cardiac reserve can be permanently diminished.^{5, 14} Angina is probably a rare sequel, but some of the reported cases are difficult to interpret.^{4, 6, 22, 23} After myocardial trauma, the quality of the heart sounds is apt to be impaired.^{7, 8, 14} There may be a gallop rhythm,^{8, 24} and if dilatation of the heart is sufficient to stretch a valvular ring, a systolic murmur may be produced.⁵

The electrocardiographic changes in contusion of heart muscle may be those usually considered diagnostic of infarction,^{15, 20, 25, 26} in either event the record is only one of the electrochemical changes accompanying focal myocardial necrosis. This should be borne in mind if a tracing is obtained on a patient with cardiac distress after an intrathoracic operation. In such a case a special effort should be made to demonstrate the more common signs of myocardial damage: progressive alteration in T waves on serial records²⁴; transient slurring and notching of the QRS deflection³; and, when injury is chiefly to subepicardial muscle, concordant elevations of the ST segments.²⁴ After a surgical procedure in the chest, however, minor changes in the electrocardiogram must be interpreted with caution.

Many disturbances in cardiac action have been noted after bodily insult. Most post-traumatic arrhythmias must be classified merely as changes in heart action following injury to the body. A few may be related to bruises or tears of the pericardium as surgeons sometimes observe changes in mechanism to accompany pericardiolysis. Damage to heart muscle probably accounts for a larger number, a variety of heart rhythms having been noted with myocardial trauma. The list includes extrasystolic arrhythmia,²⁷ auricular flutter,²⁵ auriculoventricular block,⁶ sinus tachycardia^{14, 24} and auricular fibrillation.^{13, 27} Most of these alterations develop promptly and are transient.

Arrhythmias have been noted in a small percentage of persons convalescing from pneumonectomy and lobectomy.^{9, 11} Auricular flutter, nodal tachycardia, premature auricular beats and auricular fibrillation have been encountered and in most cases the disturbance has occurred in the first postoperative week. In the reports of these arrhythmias inadvertent damage to the heart is not mentioned as a possible cause. The inciting factors suggested are shift of the mediastinum, anoxia of the myocardium and irritation of vagal fibers by suture abscesses in the bronchial stump. A further possibility is that reflexes are stimulated by operative injury to tissues at the root of the lung division of these structures causing alterations in the cardiac rhythm in animal experiments.²⁸

A similar effect has been observed in man.³⁰ It is difficult to determine the role of such factors in postoperative alterations in cardiac action, but the obvious possibility of trauma to the heart should not be forgotten.

In the first case reported above, cardiac damage was associated with a transient tachycardia and an unidentified arrhythmia. In Case 2 extensive myocardial contusion was the most likely cause of a persistent, rapid heart action. Bailey and Betts¹⁰ describe the onset of auricular flutter and fibrillation in a fifty-five-year-old man five days after right pneumonectomy for carcinoma. There is evidence that myocardial injury was sustained by this patient, for serial changes in the ventricular complex are reported. Of additional interest is a statement by Massie and Valle¹¹ that in 6 cases in which arrhythmias did not develop after pneumonectomy, the patients exhibited physical or electrocardiographic signs of cardiac difficulty that were not present preoperatively.

The heart may not be bruised frequently during operations in the thorax, but an important factor in the recognition of cardiac insult is an awareness of the possibility.¹ This has been stressed in reports on patients injured in traffic accidents and applies in the type of case under discussion. A diagnosis of cardiac injury should be suspected in any patient who maintains an unexplained tachycardia after an intrathoracic operation or in whom an arrhythmia or pericardial friction rub develops. It seems important to evaluate circulatory shock, chest pain or congestive failure occurring in the postoperative period.

When there is reason for suspicion, a glance at the anesthesia sheet from the patient's operation may be rewarding: an abrupt onset of rapid heart action suggesting a moment of cardiac insult. In the 2 cases presented the onset of tachycardia coincided with damage to the heart. If electrocardiograms are taken before and after operation in similar cases better evidence of cardiac injury may be available, especially when precordial leads can be studied.

A few therapeutic considerations deserve mention. When sinus rhythm is restored after postoperative arrhythmia, quinidine has been recommended as prophylaxis against recurrence of the disturbance in the convalescent period.⁹ A plea for its use could also be made if extrasystoles or other alterations in rhythm were thought to be due to focal damage of the myocardium, just as the drug is given to protect against ventricular fibrillation when ectopic beats are detected after myocardial infarction. If extensive damage to heart muscle could be inferred from the data, one would be inclined to prolong the period of bed rest. Chiefly, however, the treatment of injuries such as these is expectant, the emphasis being on prevention.

CASE 2 (C C H 294957) A 44-year-old man had a bronchiogenic carcinoma at the junction of the lingular and left-upper-lobe bronchi. The patient gave no history of cardiovascular disease, nor did examination reveal evidence of any. On April 29, 1948, left pneumonectomy was performed with the patient supine, an anterior incision being used. Anesthesia was maintained with intratracheal ether.

The chest wall was opened by resection of the anterior half of the left fourth rib, and when the mediastinal pleura had been incised, dissection of the root of the lung was begun. No difficulties were encountered until an attempt was made to isolate the inferior pulmonary vein. Much of this vessel had been surrounded by tumor, and to obtain a segment suitable for ligation and transection, pericardiectomy was necessary. The intrapericardial portion of the vein was overlaid by the left auricle, and until the heart was retracted anteriorly and toward the opposite side, the vein was inadequately exposed. The ring sponge usually employed for this purpose proved ineffective, and use was made of a flat metal blade covered with gauze and placed against the anterolateral aspect of the left ventricle.

Retraction was as gentle as possible, the surgical team being aware of the danger in this maneuver, but the heart was allowed to beat against the blade for a sufficient length

of time to dislodge the instrument repeatedly. During this interval, the pulse rate increased from 90 to 120 per minute, a lesser degree of tachycardia persisting thereafter. Many premature contractions also occurred, but these were quickly abolished by spraying of the pericardium with a 2 per cent procaine solution. The pneumonectomy was readily completed. During the operation, a transfusion of 2 liters of whole blood was given.

Except for the disturbance in cardiac action, resection was uncomplicated, and the patient appeared to have withstood the procedure well. Postoperative bronchoscopy revealed a tightly closed bronchial stump. To adjust the intrapleural pressure, several hundred cubic centimeters of air were aspirated from the left hemithorax, and the trachea, previously displaced to the right, returned to the midline. Approximately 5 minutes later, respirations and heart beat suddenly ceased. Artificial respiration and intracardiac administration of epinephrine were of no avail.

At autopsy (C C H 17536) the incised pericardium lay to the side of the heart. The right auricle and ventricle were dilated and engorged with blood. Over the anterolateral aspect of the left ventricle, the subepicardial fat was hemorrhagic. The underlying muscle was discolored purplish red and was softer than elsewhere, this lesion involving from the outer fifth to half of the ventricular wall and extending from the auriculoventricular groove to within 4 cm of the cardiac apex. In other regions the myocardium was a uniform reddish brown. There was slight arteriosclerosis of the cor-

onary arteries. The heart weighed 450 gm, but there were no valvular deformities.

Microscopical sections from the purplish-red focus in the left ventricle disclosed an extensive contusion. The small blood vessels were hyperemic, and the pattern of myocardial fibers was altered by foci of interstitial hemorrhage (Fig 1). In the subepicardial muscle, the fibers were fragmented and devoid of cross striations, but in adjacent tissue there were less marked alterations consisting of pyknosis of nuclei and a granular transformation of sarcoplasm. There was no infiltration of the myocardium by inflammatory cells. Sections from other portions of the heart were not remarkable.

Tumor metastases were found in the regional and retroperitoneal lymph nodes and within the liver and right adrenal gland.

The left hemithorax was free of air but contained 800 cc. of bloody fluid. The sutures in the bronchial stump and the ligatures about the pulmonary vessels were intact.

The viscera exhibited passive hyperemia.

There were no other findings of note.

Although myocardial injury was indicated by the tachycardia that persisted after cardiac retraction, this sign of muscle damage was not appreciated. It was known that the heart had been bruised superficially, but neither the extent of injury nor its possible relation to sudden death was recognized. The fatal outcome was considered due to the shift of the mediastinum that followed aspiration of air from the left hemithorax. In view of the degree of myocardial damage, however, it is difficult to attach cardinal significance to the shift that occurred. Asystole and ventricular fibrillation have been observed after experimental contusion of the heart,^{1, 3} and it is likely that one of these disturbances was responsible for the patient's death.

DISCUSSION

In these cases, the heart was damaged under special conditions, but the wounds are comparable to those in the literature of traumatic heart disease. Similar lesions are recognized as complications of penetrating and compressing injuries to the chest wall.^{4, 7, 15} Cardiac wounds have a variety of sequelae, the best known being some that implicate the pericardium: hemopericardial tamponade, serosanguineous effusion and pericarditis, either fibrinous or purulent.^{4, 8, 13, 18} Of interest is a case report of pericardial calcification and the constriction syndrome following a severe blow to the thorax.⁶ In general, there is less familiarity with the clinical course of patients whose disability is due solely to myocardial damage.

Contusion of heart muscle is responsible for an entity of wide latitude, the signs and symptoms of these injuries resembling those of myocardial infarction. The basis for this parallel is the histopathological similarity of the lesions, each exhibiting necrosis of muscle fibers, interstitial hemorrhage, leukocytic infiltration and the formation of scar tissue.¹ A contusion may produce no symptoms¹⁹ or only mild precordial discomfort.^{4, 8} Circulatory shock or substernal pain may be the dominant feature,^{6, 14} the picture resembling that



FIGURE 1 Photomicrograph of the Myocardium Injured During Pneumonectomy in Case 2

Note the interstitial hemorrhage and degree of myocardial fragmentation (hematoxylin and eosin stain $\times 112$)

bladder to empty itself. This increased pressure results in an interference with the blood supply and the lymphatic drainage, and this in turn may be followed by the development of gangrene of the organ — usually beginning in the fundus since that portion is farthest from the source of blood supply, or the stone itself may erode the edematous gall-bladder wall. The course of events then leads to perforation of the viscus, which may be of five types: perforation with communication with another viscus (usually duodenum, colon or stomach), formation of a pericholecystic abscess, acute free perforation, perforation into the liver, and external perforation. Although this entire sequence of events may be interrupted at any time if the stone becomes dislodged and the contents of the gall bladder are evacuated through normal channels, the process is usually irreversible.

PATHOLOGY

According to Hallendorf and his co-workers,² histologic evidence indicates that circulatory disturbance plays the most important role in the pathogenesis of gangrenous cholecystitis, and late evidence of infection, a rare and lesser role. Necrosis, engorgement of the venous and lymphatic systems, intramural hemorrhage and edema, with mucosal desquamation, fibroblastic activity and early lymphocytic infiltration followed by a late invasion of polymorphonuclear cells were the consistent microscopical features in their series. It is interesting that when operation was done within the first twenty-four hours of the onset of an attack, extensive edema and marked venous congestion were characteristic features.

In addition, the Boston City Hospital series of gall bladders by definition all had to show a complete necrosis of all layers of the wall in at least one area to be included in this review.

STATISTICAL REVIEW

Fifty-four females and 46 males comprised this series, a sex distribution quite in distinction to

TABLE 1 Age Distribution

Age	No of Cases
yr	
0-20	0
21-30	2
31-40	4
41-50	8
51-60	26
61-70	34
71-80	24
81-90	2
Total	100

that of acute cholecystitis, which occurs five times as frequently in females.³ Eighty-six of these patients were over the age of fifty (Table 1). Again, this is in marked contrast to the age distribution

of acute cholecystitis, which occurs in general in a younger age group. The duration of present illness before seeking hospital admission is shown in Table 2, from which it can be seen that 72 patients entered during the first week of their illness. A history of chronic gall-bladder disease was present in 90 cases. In the remaining 10 cases a history of previous attacks was not obtained either because

TABLE 2 Duration of Present Illness

DURATION	No of Cases
Not known	-
1-2 days	44
4-7 days	28
1-4 wk	11
1-3 mo	8
Over 3 mo	6
Total	100

of the advanced age or the moribund state of the patient, or because it did not exist. This is in substantial agreement with the work of Stone and Douglass,⁴ who found a history consistent with previous attacks of acute gall-bladder disease in 100 per cent of 38 cases of perforated gall bladders in their series.

The complaints of the patients and their relative frequency were listed; 96 patients (all patients who were reliable on this point) complained of abdominal pain, and 82 were able to localize this pain to the right upper quadrant. In only 26 patients was the usually described radiation of pain to the right subscapular area elicited. The remaining 14 could not localize their pain but complained of pain "all over" the abdomen, 62 of the patients were nauseated, and 60 vomited once or more during the course of their present illness. Chills and fever were found in only 7 cases. Right-upper-quadrant tenderness was demonstrated in 82 patients, and was the most prevalent sign. And generalized abdominal tenderness was found in an additional 15. A right-upper-quadrant mass was found in 61 patients, much more frequently than in other series.⁵⁻⁷

Twenty-seven patients showed varying degrees of distention as noted by the admitting physician. This finding is stressed because the presence of distention in several cases was responsible for shifting the suspicion of disease from the gall bladder to another and innocent organ. In this regard, gall-stone ileus, the result of perforation of the gall bladder into the intestinal tract, has received widespread attention in the literature. Blain and Harkins,⁸ in their series of 41 cases of gall-bladder perforation, had 11 cases (or 27 per cent of the series) associated with signs of intestinal obstruction. However, only 5 of these 11 cases were examples of classic gallstone ileus. The other 6 were produced by per-

SUMMARY

Two cases of fatal contusion of the heart during surgical procedures on other thoracic viscera are reported. These examples of inadvertent cardiac damage merit attention in view of the great volume of intrathoracic surgery being performed. The prevention of such wounds depends upon an awareness that they are occasionally produced, and to favor the recognition of other injuries of this type, some aspects of cardiac trauma are reviewed.

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ACUTE GANGRENOUS CHOLECYSTITIS

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GANGRENE of the gall bladder is a complete necrosis of a portion of the wall in one or more areas, and is frequently followed by perforation. Since 1844, when James Duncan,¹ of the Royal Infirmary in Edinburgh, reported a case, the clinical application of the pathology of this disease has been a source of interest and concern to internists and surgeons. And particularly in recent years the question of the proper time for surgical intervention has been much discussed.

This paper is a report of 100 consecutive cases of acute gangrenous cholecystitis at the Boston City Hospital, where the character of the gall bladder was adequately described by the surgeon, or the specimen clearly reported by the pathologist, or where the patient ultimately came to post-mortem examination. The pathology had to be quite precise to be included in this series. In cases in which a cholecystostomy only was done, the character of the gall bladder had to be adequately described at some length so that no confusion regarding the nature of the pathology existed. In short, cases in which the operative note failed to supply ade-

quate knowledge about the organ were not included in this series. When the organ was removed or when the patient came to autopsy examination, the gross and microscopical report of the pathologist formed the basis for inclusion. The etiology and the pathogenesis of acute gangrenous cholecystitis are reviewed below, and a statistical analysis of this series of cases is reported because the results are sometimes at variance with previously published statistics, because it appears that acute gangrenous cholecystitis as a clinical entity per se is not generally appreciated and because further emphasis on the lethal nature of the disease seems necessary.

ETIOLOGY

Attacks of acute biliary colic result from obstruction of the cystic duct, usually by a stone rather than by any primary inflammatory condition. Irrespective of what creates the first obstruction, it is apparent that profound vascular and lymphatic stasis may occur so abruptly that virtual infarction ensues. Acute obstruction leads to increased intravisceral tension, and colicky pain results from the strenuous efforts of the muscular gall

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bladder to empty itself. This increased pressure results in an interference with the blood supply and the lymphatic drainage, and this in turn may be followed by the development of gangrene of the organ — usually beginning in the fundus since that portion is farthest from the source of blood supply, or the stone itself may erode the edematous gall-bladder wall. The course of events then leads to perforation of the viscus, which may be of five types: perforation with communication with another viscus (usually duodenum, colon or stomach), formation of a pericholecystic abscess, acute free perforation, perforation into the liver, and external perforation. Although this entire sequence of events may be interrupted at any time if the stone becomes dislodged and the contents of the gall bladder are evacuated through normal channels, the process is usually irreversible.

PATHOLOGY

According to Hallendorf and his co-workers,² histologic evidence indicates that circulatory disturbance plays the most important role in the pathogenesis of gangrenous cholecystitis, and late evidence of infection, a rare and lesser role. Necrosis, engorgement of the venous and lymphatic systems, intramural hemorrhage and edema, with mucosal desquamation, fibroblastic activity and early lymphocytic infiltration followed by a late invasion of polymorphonuclear cells were the consistent microscopical features in their series. It is interesting that when operation was done within the first twenty-four hours of the onset of an attack, extensive edema and marked venous congestion were characteristic features.

In addition, the Boston City Hospital series of gall bladders by definition all had to show a complete necrosis of all layers of the wall in at least one area to be included in this review.

STATISTICAL REVIEW

Fifty-four females and 46 males comprised this series, a sex distribution quite in distinction to

TABLE 1 *Age Distribution*

AGE	No. of Cases
yr	
0-20	0
21-30	2
31-40	4
41-50	8
51-60	26
61-70	34
71-80	24
81-90	2
Total	100

that of acute cholecystitis, which occurs five times as frequently in females.³ Eighty-six of these patients were over the age of fifty (Table 1). Again, this is in marked contrast to the age distribution

of acute cholecystitis, which occurs in general in a younger age group. The duration of present illness before seeking hospital admission is shown in Table 2, from which it can be seen that 72 patients entered during the first week of their illness. A history of chronic gall-bladder disease was present in 90 cases. In the remaining 10 cases a history of previous attacks was not obtained either because

TABLE 2 *Duration of Present Illness*

DURATION	No. of Cases
Not known	3
1-3 days	44
4-7 days	28
1-4 wk.	11
1-3 mo	8
Over 3 mo	6
Total	100

of the advanced age or the moribund state of the patient, or because it did not exist. This is in substantial agreement with the work of Stone and Douglass,⁴ who found a history consistent with previous attacks of acute gall-bladder disease in 100 per cent of 38 cases of perforated gall bladders in their series.

The complaints of the patients and their relative frequency were listed; 96 patients (all patients who were reliable on this point) complained of abdominal pain, and 82 were able to localize this pain to the right upper quadrant. In only 26 patients was the usually described radiation of pain to the right subscapular area elicited. The remaining 14 could not localize their pain but complained of pain "all over" the abdomen; 62 of the patients were nauseated, and 60 vomited once or more during the course of their present illness. Chills and fever were found in only 7 cases. Right-upper-quadrant tenderness was demonstrated in 82 patients, and was the most prevalent sign. And generalized abdominal tenderness was found in an additional 15. A right-upper-quadrant mass was found in 61 patients, much more frequently than in other series.⁵⁻⁷

Twenty-seven patients showed varying degrees of distention as noted by the admitting physician. This finding is stressed because the presence of distention in several cases was responsible for shifting the suspicion of disease from the gall bladder to another and innocent organ. In this regard, gall-stone ileus, the result of perforation of the gall bladder into the intestinal tract, has received widespread attention in the literature. Blain and Harkins,⁸ in their series of 41 cases of gall-bladder perforation, had 11 cases (or 27 per cent of the series) associated with signs of intestinal obstruction. However, only 5 of these 11 cases were examples of classic gallstone ileus. The other 6 were produced by per-

foration with resulting inflammatory or paralytic ileus or mechanical obstruction as by adhesions. In this series there were 4 cases of proved gallstone ileus, and 23 cases of paralytic ileus produced in a fashion comparable to that described in the last group of Blain and Harkins.⁹ These cases will be reported in detail later. Distention, then, on either basis is not uncommon in gangrenous cholecystitis.

Jaundice was present in only 9 cases and was obviously of little diagnostic significance in this

TABLE 3 *Temperature and Pulse*

TEMPERATURE °F	NO. OF CASES	PULSE	NO. OF CASES
98.6-99	29	60-80	17
99.2-100	25	81-90	25
100.2-101	18	91-100	38
101.2-102	22	101-120	18
102.2-103	3	121-140	2
103.2-104	5		
Totals	100		100

condition. The majority of patients (69) had white-cell counts ranging from 10,000 to 25,000. The temperature and pulse ranges are shown in Table 3.

Eighty-five patients had perforations at the time of examination, or evidence of previous perforation such as localized abscesses, gallstones within the lumen of the intestine, stones free in the abdominal cavity, free generalized peritonitis and multiple and recent adhesions indicative of recent perforation. Eighty-five patients showed peritonitis, and in 23 cases in this group a generalized peritonitis was observed. The remaining 62 patients had well demonstrated evidence of the body's attempts to define and restrict the spread of infection, such as adhesions or omentum walling off the perforated viscus and resulting in a localized type of peritonitis.

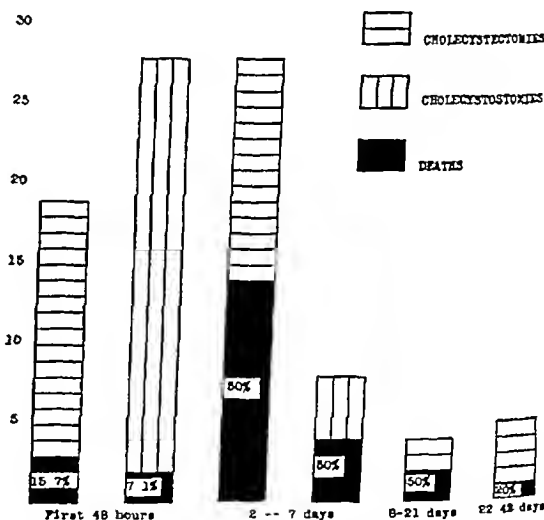
Acute free perforation carries a mortality three times that of localized peritonitis.⁴ Fortunately, free perforation is less frequent than localized peritonitis.⁹ This is explained on the basis of the position of the gall bladder sheltered as it is by the liver, because of the inherent distensibility of the organ, and because the omentum is accessible and readily mobilized to envelop the affected viscus. For these reasons acute gangrenous cholecystitis is not an emergency of the high order of acute appendicitis. Nevertheless, free perforation occurred often enough in this series to warrant its serious consideration by the attending surgeon in deciding to operate.

Stones were present in 89 patients in this Boston City Hospital Series. Ninety-eight per cent of the Mayo Clinic Series showed stones in the gangrenous gall bladder or cystic duct, and Hallendorf² points out that this high percentage was the result of a careful search of the edematous and distorted specimen for stones that had been overlooked by the surgeon or the pathologist on the day of operation.

It is my impression that the more carefully the specimen is searched for stones, the more frequently they will be discovered. Most investigators^{5, 10, 11} agree that gangrene and perforation rarely occur except in association with stones.

Figure 1 shows the mortality figures in this series of 100 cases. Several striking facts are immediately apparent. In this particular series 8 patients not coming to operation died. This figure may be misleading, for in a check of the records of these patients it is noted that at least 6 and possibly 7 were in extremis on entry, or had severe concomitant disease, and it appears in retrospect that the surgeons based their decision not to operate on the firm conviction that the patient was beyond human succor. Three of these patients refused surgery.

Among the 47 patients operated on within the first forty-eight hours of their present illness, there

FIGURE 1 *Mortality in 100 Cases of Acute Gangrenous Cholecystitis*

were 5 deaths, 3 after cholecystectomy, and 2 after the less radical procedure of cholecystostomy — a mortality of 10.6 per cent in this group. From this time until the beginning of the third week 40 patients were operated on, and the over-all mortality of this group was 50 per cent irrespective of the type of surgical procedure elected.

Again, the mortality dropped appreciably in the group of cases coming to operation within the third to the sixth week, with 1 death among 5 cases — a mortality of 20 per cent.

DISCUSSION

Of all cases of acute cholecystitis 13 to 24 per cent go on to gangrenous cholecystitis,^{12, 14} which should negate the contention that perforation is a rare and seldom fatal complication. In 12,000 consecutive routine autopsies at the Los Angeles

County Hospital 1 in 375 persons succumbed to a perforated gall bladder.⁹

The treatment of this disease is surgical. In the etiology of cholecystitis infection plays a late and minor role.^{16,17} Furthermore, it has been shown experimentally in dogs¹⁸ that sulfonamides given parenterally will not be recovered from the gall bladders of animals whose cystic ducts are completely obstructed. Zaslow, Counsellor and Heilman¹⁹ have proved the same lack of recovery in human beings with penicillin and streptomycin. This is a significant observation, since in most cases of acute cholecystitis and in all cases of acute gangrenous cholecystitis obstruction of the cystic duct is present. Therefore, the value of these drugs is definitely limited in cases in which obstruction is present.

The mortality of acute cholecystitis is commonly in direct proportion to the percentage of gangrene and perforation. It seems better judgment to operate on all patients with acute cholecystitis early — that is, within the first forty-eight hours if possible, and at least as soon as they have been adequately prepared. Indeed, this view is now maintained by surgeons of large experience with this disease.^{4,9,12,20-22}

The over-all mortality in this Boston City Hospital Series was high (34 per cent), the mortality for those operated on was 28.2, and that for the group not operated on was 100 per cent. The advanced age of the patients, with the frequent association of acute gangrenous cholecystitis and degenerative diseases, particularly the cardiovascular diseases, and the generally poor state of nutrition of these older people tend to raise both the morbidity and the mortality. The mortality, however, is a largely preventable one. When it is realized that gallstones are never benign, that gall bladders containing them should be removed promptly and that patients with acute gangrenous cholecystitis should be promptly operated on the mortality figures should be lowered considerably.

Early adequate preoperative preparation, proper anesthesia, quick and gentle surgery and careful postoperative care by surgeon and internist will also lower the mortality substantially. Most surgeons^{2,10} agree that whenever possible a cholecystectomy should be performed. If in the judgment of the surgeon the general condition of the patient will not stand this procedure, the less desirable cholecystostomy should be elected.

In the Boston City Hospital Series almost 75 per cent of the patients presented themselves early in the course of the present illness, which leads one to believe that by earlier recognition of this entity of gangrenous cholecystitis, prompt operation with its lowered mortality may be offered more frequently to these patients.

Proceeding further with this course of reasoning one might postulate that all diseased gall bladders,

especially those with stones, should be removed early. The myth of "silent stones" is gradually disappearing in the face of accumulating statistics.

SUMMARY

The etiology and pathogenesis of acute gangrenous cholecystitis are briefly reviewed.

Acute gangrenous cholecystitis occurs almost equally in males and females, usually over the age of fifty, who often have a past history of biliary disease of long standing. Their chief complaint is pain in the right upper quadrant, frequently with nausea and vomiting. Right-upper-quadrant tenderness, a mass in the same location and an elevated temperature, pulse and white-cell count complete the clinical picture.

Perforation is a frequent late complication occurring almost invariably in gall bladders with stones.

The lowest mortality of all groups in this series, operative and nonoperative alike, was found in patients operated on within the first forty-eight hours of entry.

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KAPOSÍ'S VARICELLIFORM ERUPTION*

Report of a Case

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IN 1944 Dr Herbert A. Wenner¹ wrote "The integument of infants and children ill with eczema is frequently infected by bacterial opportunists and less frequently by filtrable viruses." The former is easily recognized, the latter, because of its infrequent occurrence may easily be overlooked. The case presented below is that of an eight-month-old baby who had had intractable atopic eczema since the age of six days. At the age of eight months his eczema became complicated by the disease now known as Kaposi's varicelliform eruption, which is said to be due to a filtrable virus.

This skin disease was first described by Kaposi² in 1887, who depicted it as "an alarming complication of infantile eczema." Although at that time it failed to attract wide attention, it has aroused great interest in recent years. Thus, one now finds a considerable number of cases described in the pediatric, dermatologic and allergic literature.

CLINICAL DESCRIPTION

The features of Kaposi's varicelliform eruption are striking. The original description by Kaposi was vividly repeated in the case presented below. Almost all the reported cases have occurred in infants and young children, although the disease has also been reported in adults.^{3,6} Invariably, there is a pre-existing atopic eczema. The frequent coexistence of allergic eczema and Kaposi's varicelliform eruption is probably coincidental and may be accounted for by the fact that in young children atopic eczema is by far the most chronic and the most frequent skin disease. In a review of 67 cases of Kaposi's varicelliform eruption by Barton and Brunsting⁵ in 1944 only 53 occurred in patients having pre-existing allergic dermatoses. The remaining 14 patients had nonallergic skin diseases.

Typically, the disease manifests itself with an elevated temperature, which reaches 105°F on occasion and may remain elevated for eight to twelve days. There is restlessness and prostration. Nausea and vomiting or diarrhea, or both, may occur. Intense pruritus is a constant finding. The skin lesions occur early on the pre-existing eczematous sites, and only later invade adjacent intact skin. The lesions are discrete vesicles and range

from 2 to 3 mm in diameter. They appear in crops, may become umbilicated and may assume a dark-brown discoloration. The vesicles contain clear fluid, except when, as a result of external contamination, infection renders them turbid. Sometimes, a number of vesicles, especially near skin folds or near the mouth, coalesce, break down and form large, bleeding, raw, granular surfaces (Fig. 1). Complete remission of the acute process takes place in all patients who survive. The lesions fade away



FIGURE 1 Photograph Taken on the Tenth Day of the Disease, Showing the Large Granular Bleeding Surface in the Left Popliteal Space

after about two weeks, leaving, however, the original eczema to plague patient and doctor alike.

Complications have been reported. These include bronchopneumonia, suppurative lymphadenitis, otitis media and alopecia.

Fatal cases do occur. Fries,⁶ reviewing 82 cases in the literature, states that in these there was a 20 per cent mortality. In a recent New York City epidemic of 43 children, 2 died, giving a mortality of 4 per cent. Wenner¹ reports 1 death in his 3 cases. McLachlan,⁷ in 1936, reported 5 deaths in 16 cases — a mortality of 31 per cent.

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ETIOLOGY

Until recent years the etiology was obscure. Kaposi² frankly stated that he was "ignorant of its causation." A variety of infectious agents have been under suspicion. Pyogenic staphylococcus, streptococcus, fungi and, recently, filtrable viruses have been implicated. Existing evidence, however, favors the idea that certain strains of filtrable viruses will, when conditions are favorable, invade the body of a patient ill with eczema and produce this disease. The specific virus involved is controversial: some observers implicate the virus of vaccinia, and others the virus of herpes simplex.

Fries et al.,⁶ in 1948, reported 16 cases of Kaposi's varicelliform eruption. All 16 cases occurred in eczematous babies. These cases were part of an epidemic of 43 cases of Kaposi's varicelliform eruption that occurred in New York City in 1947. As will be recalled, New York City conducted a mass vaccination program in 1947 in which 6,350,000 persons were vaccinated against smallpox. The outbreak of this disease started three weeks after the program began, and ended three weeks after the program was completed. It is interesting to note that none of the 16 patients discussed by Fries had been vaccinated prior to the outbreak, and when vaccination was attempted after recovery, all gave immune reactions. These facts appear to implicate the virus of vaccinia as the etiologic agent.

In 1941 Ronchese⁵ reported 2 cases of this disease, which he also believed to be caused by the virus of vaccinia. He argued against the virus of herpes simplex, and asked "Why is herpes simplex so common and Kaposi's varicelliform eruption so rare?" and "Why does Kaposi's varicelliform eruption not recur, whereas recurrences are characteristic of herpes simplex?"

In recent years, however, a number of observers^{1, 4, 9, 10} have succeeded in identifying the virus of herpes simplex from the vesicular lesions in a significant number of cases. An exhaustive study on the etiology of this disease was presented by Wenner¹ in 1944. He observed 3 infants who had infantile eczema complicated by Kaposi's varicelliform eruption. He was able to isolate a filtrable virus in the cutaneous lesions of all the infants, and in the brain of one who died of the disease. From serologic studies and from immunization studies done on rabbits he concluded that the viruses thus isolated were "closely related with the virus of herpes simplex."

In 1947 Ruchman, Welsh and Dodd⁹ reported 4 cases of Kaposi's varicelliform eruption, and in each the virus of herpes simplex was recovered from the cutaneous lesions. In 1948 Ruchman and Dodd⁴ reported 5 additional cases. In 3 the virus of herpes simplex was isolated. In the remaining 2 cases,

in which isolation of the virus was unsuccessful, the antibody titer against herpes simplex rose during convalescence. These authors consider the virus of herpes simplex the etiologic agent.

In 1947 Barker and Hallinger¹⁰ and in 1948 Ruchman and Dodd⁴ called attention to the wide range of infections in which, in recent years, the virus of herpes simplex has been demonstrated.¹¹⁻¹⁵ In the study of Barker and Hallinger the suggestion is made that cases of Kaposi's varicelliform eruption in which the virus of herpes simplex is demonstrated should be named systemic herpes simplex, rather than Kaposi's varicelliform eruption. In the opinion of these authors the latter represents a "wide variation of a syndrome," whereas these virus infections produce definite systemic symptoms in addition to diffuse cutaneous manifestations.

After reviewing the literature, we have reached the conclusion that although the clinical features of this disease are well defined, the causative agent may vary in different cases. Thus, the syndrome of Kaposi's varicelliform eruption may be caused by the virus of herpes simplex or vaccinia, or even by a virus as yet unidentified. In the final analysis it is the identification, by laboratory methods, of the specific virus involved that determines the exact etiologic agent.

CASE REPORT

G. R., a 7-month-old male infant, entered the Rhode Island Hospital on November 8, 1948, because of an unusual skin eruption, accompanied by an elevated temperature of 8 days' duration. The mother stated that the rash was "entirely new and different from the old eczema, which he has had all his life."

The family history was not remarkable. There were 8 siblings. The parents and siblings were well and had always been free from allergic manifestations.

The baby was full term, delivery was normal, and the birth weight was 9 lb., 14 oz. Atopic eczema was noticed at the age of 6 days, first appearing on the face, and quickly spreading to the shoulders, arms and legs. The lesions were always severe and had persisted until the admission, with only brief periods of incomplete healing now and then. There were no other prior illnesses. He had not been inoculated against any contagious disease. There was no contact with a recently vaccinated person. Skin tests produced minimal reactions (erythema but no whealing) to cow's milk and egg white and a negative reaction to wheat. In spite of extensive dietary manipulations, during which milk, wheat and eggs were excluded, there was no sustained improvement in the eczema. Development and nutrition, however, were normal. On two previous occasions the baby had been hospitalized for eczema, but only temporary improvement had resulted each time.

The present illness had begun with an elevated temperature and with the appearance of an unusual rash, which was superimposed upon the pre-existing eczema.

Physical examination revealed a well developed and well nourished infant who exhibited constant scratching. The throat was normal. The eardrums were bright red but not bulging. The posterior cervical lymph nodes were soft and measured 0.5 cm in diameter. The inguinal and axillary lymph nodes were somewhat enlarged. Cardiac rhythm and sounds were normal. The lungs were clear. The abdomen and extremities showed no abnormalities.

The skin lesions, when they first appeared, consisted of discrete raised flecks of ecchymosis, and occurred on the face only. In a day or two the lesions became vesicular, larger and more raised, and extended to all sites of the pre-existing eczema. Many but not all of the vesicles showed brownish

discoloration (Fig 2) In a few areas, especially those about the mouth and natural body creases, the vesicles had ruptured and had become confluent, producing large bleeding surfaces The contents of the vesicles were serous and not purulent Later, a few of the vesicles invaded neighboring healthy skin Beneath the lesions thus described was the old oozing eczema The temperature ranged between 101 and 105°F and continued for about 12 days

The height of the disease was reached on the 7th day after the onset, when the patient appeared to be very listless and

cent neutrophilic myelocytes Examination of the urine showed a specific gravity of 1.022, with a pH of 5, a trace of protein and sugar and a positive acetone reaction Smears made from the vesicular exudates demonstrated a rare pus cell, a rare gram-positive coccus and a rare gram-negative rod (the latter two were considered contaminants) A culture taken of the exudate produced a growth of *Staphylococcus aureus*, coagulase positive (This was thought to be a skin contaminant) A blood culture was reported positive for *Staph. albus*, coagulase negative No facilities were available for virus studies

DIAGNOSIS AND TREATMENT

The diagnosis of Kaposi's varicelliform eruption is easily made, when one remembers the clinical features, the characteristic lesions and the almost exclusive occurrence in eczematous children The treatment is symptomatic and supportive Special attention should be given to the prevention of scratching This requires careful restraining of arms and legs, and a minimum of bedclothes We found that a covered cradle placed over the trunk and extremities was helpful The gentle application of a suitable mild antipruritic lotion, such as phenolized calamine lotion, or a drying agent such as Burow's solution 1:40, will also help The use of antibiotic drugs, such as penicillin, we think is indicated, not against the prevailing virus organism but for the protection against complications Although the disease is not considered to be contagious, direct contact should be avoided, and in the hospital, barrier technic should be instituted *

SUMMARY

Another case of Kaposi's varicelliform eruption is herewith presented The diagnosis was made on the basis of its clinical features The prevailing views on its etiology are reviewed

It is believed that if this rare condition is kept in mind the diagnosis will be made without much difficulty It is likewise thought that by the employment of antibiotic drugs, complications and deaths will be avoided

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Fries recently mentioned a communication from Dr. Marion B. Sulzberger, who reported the demonstration by Baer and Miller of the effectiveness of local and systemic administration of aureomycin in 2 severe cases of Kaposi's varicelliform eruption that were presumably due to the virus of herpes simplex

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FIGURE 2 Photograph Taken on the Twelfth Day of the Disease, Showing Numerous Discrete Vesicles, Many of Which Are Brownish
Atopic eczema is seen in the background

prostrated, and the temperature rose to 105°F On the 8th day the patient was hospitalized On the 8th day also, parenteral administration of penicillin was begun, 300,000 units of crystalline being given daily for 4 days On the 11th day of the illness, or the 4th hospital day, the vesicles showed signs of beginning involution, and from then on improvement was rapid By the 15th day the vesicular lesions had practically disappeared Only the original eczema remained, and this also showed considerable improvement

Initial examination of the blood soon after admission revealed a red-cell count of 4,180,000 with a hemoglobin of 11 gm per 100 cc, and a white-cell count of 14,000, with 51 per cent neutrophils, 45 per cent lymphocytes and 4 per cent monocytes Four days later, on the 12th day of illness, the red-cell count was 3,300,000, with a hemoglobin of 10.2 per 100 cc., and a white-cell count of 30,000, with 21 per cent neutrophils, 70 per cent lymphocytes, 3 per cent monocytes, 4 per cent eosinophils, 1 per cent basophils and 1 per

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MEDICAL PROGRESS

MECHANICAL AND THERMAL INJURY FROM THE ATOMIC BOMB*

HERMAN E. PEARSE, M.D.,† AND J. THOMAS PAYNE, M.D.‡

ROCHESTER, NEW YORK

THE energy released by the explosion of an atomic bomb is of a degree unsurpassed by anything known to man. In addition to large amounts of radioactive energy, great quantities of thermal and mechanical energy are released. It is the latter two that cause the great physical damage and large numbers of casualties. Photographs of

Radiation injury is not considered here. This arbitrary separation of the medical effects of the bomb makes the approach to the problems raised more simple, but it should be borne in mind that one person may have all three types of injury and, as pointed out by Parsons,⁴ can be killed "three times over." For purposes of clarity, therefore, the remainder of this paper is devoted only to the traumatic and thermal effects of the bomb.

Trauma of the primary type, due to blast alone (Table 1) is difficult to evaluate. Apparently the

TABLE 1 *Types of Injury from Atomic-Bomb Explosions*

TYPE OF INJURY	ESTIMATED PERCENTAGE TOTAL PER TYPE OF INJURY ^{1,2}	TOTALS ³
Radiation	Over 30	15
Primary		
Secondary		
Trauma	70	
Primary — direct result of blast		
Secondary — flying debris such as glass and collapsing buildings		
Fractures	11	85
Lacerations (Ninoshima Hospital ²)	37	
Contusions	52	
Burns	65-85	
Flash	92	
Secondary		

the destruction done by the atomic bombs in Japan emphasize the magnitude of the mechanical and thermal effects, and give mute evidence of the human demoralization and disorganization that takes place after such catastrophes.

Injuries to personnel from the atomic-bomb explosion have been divided into three categories: radiation injury, trauma and burns (Table 1).

*From the Department of Surgery, University of Rochester School of Medicine and Dentistry.

This paper is based on work performed under contract with the United States Atomic Energy Commission at The University of Rochester Atomic Energy Project, Rochester, New York.

This paper is adapted from lectures that were given on January 27 and April 7, 1949, for the Medical Indoctrination Course, Armed Forces Special Weapons Project, and are to be published by the Government Printing Office in the *Radiological Defense Manual*, Volume III.

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‡Instructor in surgery, University of Rochester School of Medicine, resident surgeon, Strong Memorial and Rochester Municipal hospitals.

ATOM BOMB BLAST DAMAGE

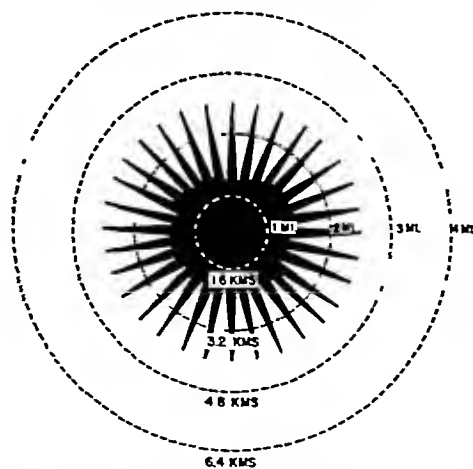


FIGURE 1 *Relatively Constricted Zone of Damage (in Black), Which Should Be Compared to the Spread of Thermal Effects (Fig 3)*⁵

blast did not have the trip-hammer effect of other high explosives but was more like a sudden, violent gust of hot air, which lasted over a relatively long period.⁵ Pulmonary and other visceral blast effects were not noted, nor was the incidence of perforated eardrums excessively high.¹

The distribution and amount of secondary trauma were dependent on the distance from the ground center of the explosion. Figure 1 illustrates the approximate zones of damage. Within a radius of 2.4 km, there was complete collapse of the native wooden buildings. Within this zone, the incidence

explained by the fact that they were relatively minor, and permitted the patient to seek treatment

ATOM BOMB THERMAL DAMAGE

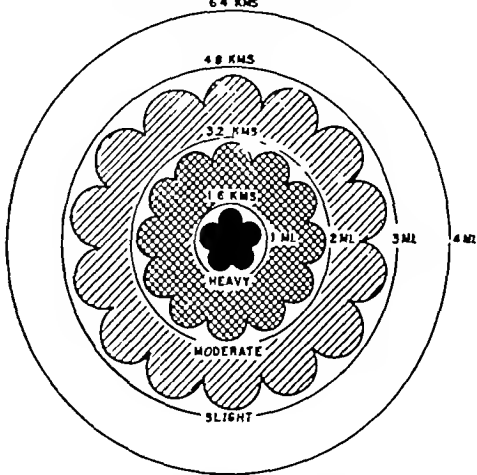


FIGURE 3 Range of Thermal Damage, Which Was Probably the Greatest of That Due to Any of the Forces Unleashed by the Atomic-Bomb Explosion (Compare this with Figure 1³)

The lacerations were of interest in that they were largely due to flying glass fragments. These frag-



FIGURE 2 Scarring Resulting from Multiple Lacerations Caused by Flying Glass Fragments, As Photographed Some Twenty-One Months after Injury

The wounds were probably infected as evidenced by the wide scars. (Photograph by Signal Corps, United States Army)

of mechanical injury was very high, dropping off gradually to less than 14 per cent beyond 2.7 km.⁵

The injuries consisted of fractures, lacerations and contusions. The low incidence of fractures — at least in the hospital given as the usual example (Table 1)

TABLE 2 Components of Atomic-Bomb Flash⁵

Temperature	Estimated at over 4000 C
Transmission	Largely by radiation
Spectrum	High in ultraviolet High in infrared High in visible light and brilliancy
Duration	Less than a second

— is probably because persons with major fractures were unable to seek treatment, or perished in the collapsed buildings. There is no evidence that these fractures were unusual in any respect. The contusions did not seem to be remarkable. The high incidence reported for these injuries is probably



FIGURE 4 Flash Burn of Moderate Severity and Extent, Photographed Early in the Course of Healing

The distribution of the lesion shows that the patient was walking in an axis, perpendicular to the explosion, with the right side facing the bomb, the left arm swinging forward, to expose the medial surface, and the right arm hanging down by the side. The lack of burning in the sternal depression demonstrates the effect of even the little protection afforded by the protrusion of the right anterior chest wall. The eyes were not severely damaged, the swelling probably being attributable to the inflammatory effects of adjacent burns. (United States Army Medical Museum)

ments were so small that clothing protected the patient in some cases. In other circumstances

fragments were of such size as to make removal difficult. Multiple lacerated wounds were very common (Fig 2).

The exact amount of morbidity and mortality attributable to the traumatic factor in the Japanese explosions will probably never be known, because, immediately after the blasts, fire and disorganization prevented adequate and early rescue measures. It seems reasonable, however, to suppose that both the morbidity and mortality from the traumatic factor could be greatly reduced by a properly organized and functioning rescue system instituted early. Once the casualty is in the hands of medical personnel, treatment itself should present no unique problem other than that of materiel. It might be

The largest and most important category (numerically) of atomic-bomb injury is the burn. This group of injuries also can be divided into primary (due to the bomb, per se) and secondary (due to burning buildings and so forth) (Table 1). Tsuzuki⁶ estimated that about 90 per cent of patients treated within the first few days were burned. LeRoy² estimated that less than 5 per cent of the



FIGURE 5. Mild Flash Burn of Exposed Portions of the Skin, As It Appeared Sixty-Three Days after the Nagasaki Explosion. The protected portions are outlined by the undershirt. The burned portions of the face, shoulders and arms were of "walnut-stair" color.⁷

important to treat these cases (particularly the lacerations) vigorously and in a definitive manner, all possible effort being made to effect healing within the first two weeks, for thereafter, the major effects of irradiation sickness begin to appear. Even though the casualty received a sublethal dose of ionizing irradiation, his unhealed wounds would break down, infection would supervene, and death might ensue from a relatively minor injury.



FIGURE 6. Residue of a Mild Burn with Color Changes between the Burned Area and the Area Protected by the Slip, Photographed Two Years after Burning.

Note the scarring beneath the right scapula where the skin was burned through adherent or moist clothing. (Photograph by Signal Corps, United States Army.)

burns were caused by the fires in buildings and debris. There then remains a group consisting of about 85 per cent of all casualties treated within the first week who were suffering from primary atomic-bomb burns.

The energy that produced this high incidence of primary burns had certain characteristics. The heat was intense, and largely radiant, with extremely high ultraviolet, visible and infrared components. The exposure was very brief⁸ — probably less than a second (Table 2).

As with the traumatic factor, the thermal effects were closely related to the distance from the ground center of the explosion (Fig 3), but had a longer radius. This explains the high incidence of severe burns uncomplicated by blast or ionizing irradiation. These are the reparable casualties.

Because the thermal energy was largely radiant, effects were modified by shading of buildings, and the angle of incidence of energy. Clothing served as sufficient protection in some cases; light-colored

clothing being better than dark, however, if the clothing was adherent to the skin by perspiration, burning occurred even through this protection.

The burns produced were of varied severity and distribution. "Profile" burns were common (Fig 4), the parts directly exposed to the flash being burned most severely. Mild burns occurred, without vesication. These burns might be sustained beyond 3 km from the center and were intensely erythematous within the few days immediately after exposure. However, they gradually became



FIGURE 7 Contracture and Ulceration, Resulting from an Inadequately Treated Flash Burn on the Dorsum of the Right Arm. Photographed Two Years after Burning⁵ (Photograph by Signal Corps, United States Army)

pigmented finally attaining a "walnut-stain" hue. This was most commonly seen on the face and therefore was called the "mask of Hiroshima." The pigmentation began to fade within a few months in some persons but in others has persisted for years⁶ (Fig 5).

More severe burns, corresponding to second-degree, moderate temperature burns, were frequent, but apparently did not carry the high mortality for large areas seen in the latter type of burn (Fig 4). Vesication was present, and often appeared within a matter of minutes. More severe burns were sustained, and complete transfascial burns were found among the dead.

The course of these burns was, in some cases, benign, many healing with little or no treatment, despite some superimposed radiation sickness. However, the healing was more often arrested, or the burn turned to a serious one by the subsequent lack of treatment and resulting complications. The sequelae were remarkable for the large number of contractures and the high incidence of keloids (Fig 6, 7 and 8) — higher than that noted in flame burns in Tokyo and other Japanese cities.⁸ Both these complications may well have been due

to the lack of adequate treatment and the extremely poor nutritional state of the people. These keloids seem to become inactive with the passage of time.

The low incidence of flame burns has been explained on the basis of the time lag between the bomb burst and the onset of fires. It is said that people escaped the fires if they were not severely injured. Those trapped in burning buildings perished, and no reliable figures are available on their number.

The care of a single traumatic or burned casualty, or a small group of casualties of such types as might result from an atomic-bomb explosion, would present somewhat of a problem. Certain essential supplies and facilities would be required. These



FIGURE 8 Keloids Following an Extensive Flash Burn of the Back, Photographed Twenty Months after the Injury^{5,8}. The uneven distribution of the keloid over the burned area is characteristic. (Photograph by Signal Corps, United States Army)

would include surgical dressings of all types, morphine and sedatives and so forth, antibiotics and similar agents, whole blood and plasma, hospitalization or adequate shelter of some type, or both, medical and technical personnel. The volume of materiel and the number of personnel required to treat a single severely burned patient (approximately 40 per cent of the body surface) in a modern hospital is illustrated in Fig 9. Many such patients do not survive, despite this treatment.

The figures given for casualties at Hiroshima and Nagasaki are presented in Table 3. From these

it can be calculated that the severely burned group alone, at Hiroshima, probably exceeded 34,000. If it were necessary to treat all these cases in a manner similar to the case illustrated in Figure

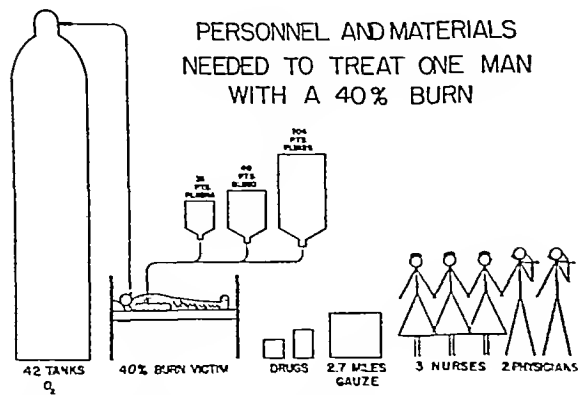


FIGURE 9 Composite Representation of Materials and Personnel Required in the Treatment of One Patient with a 40 Per Cent "Moderate-Temperature" Burn
Data represent the actual situation for a patient treated in a university hospital in the summer of 1947. Subsequent hospitalizations for corrective measures are not included in this diagram.

9 the requirements in personnel and equipment would be staggering (Fig 10). It seemed important, therefore, to re-evaluate the modern therapy of burns, in terms of the burns produced by the atomic bomb. This lesion has been called the flash burn. It is produced by a wave of radiant heat of extremely high intensity, applied over a very brief period. Experimentally, various types of burns have been defined. It has been found that the more intense the heat source, the briefer the period required to produce a burn of a given severity. This is shown graphically in Figure 11, and has been worked out in some detail for the lower-temperature zones, by Henriques and Moritz.⁹ However, the darkened area (adjacent to the question mark) represents the flash zone, and is now being studied in detail in the laboratory. Experimentally, many problems arise in the production of flash burns in the laboratory. The

TABLE 3 Atomic-Bomb Casualties²

GROUP	NO. AT HIROSHIMA	NO. AT NAGASAKI
Population	300,000	200,000
Dead	80,000	40,000
Injured	40,000	25,000
Patients in need of immediate care	85,000	50,000

search for a suitable source is one of the most difficult. Certain criteria must be met to produce an ideal flash: transient duration on the order of 0.1 second, extremely high intensity of a known degree,

a known or obtainable spectral distribution, and safety and convenience of handling. Three general principles of flash production were tried: the release of electric energy from a bank of condenser to create a flash, the creation of a constant high-intensity source directed upon a target for known intervals by means of a shutter or trip mechanism, and the use of substances that burn rapidly with an intense flame. The various sources tried, with appropriate comments, are listed in Table 4. The flash produced by burning magnesium powder has been used clinically to produce a burn, and this agent was therefore chosen.¹¹ The burns produced by the burning magnesium flash have several interesting characteristics, which are strikingly demonstrated in the histologic picture. Most

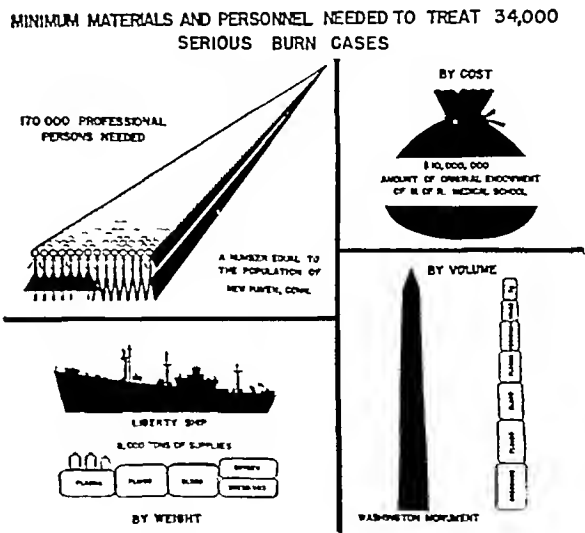


FIGURE 10 Multiplication of the Data in Figure 9 by an Estimated Number of Severe Burns from an Atomic-Bomb Explosion over a City of 300,000.

remarkable is the abrupt and diagrammatic demarcation between burned and normal skin. The normal, basophilic epidermal cells change on a straight line, to the acidophilic burned cells, which have all the characteristics of thermal injury (Fig 12). In the deeper skin, this demarcation is at the burn border, in the crypts and hair follicles. It is present in the dermis but is less easily demonstrated. There is no gradual transition zone as in the moderate temperature burns. Another characteristic of the flash burn is the method of healing. The burn of the epidermis and dermis represents a coagulative, "fixed" type of necrosis, with eschar formation and subsequent sequestration, rather than the organization seen in the noncoagulative necrotic tissue of the moderate temperature burn.

clothing being better than dark, however, if the clothing was adherent to the skin by perspiration, burning occurred even through this protection.

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FIGURE 8 Keloids Following an Extensive Flash Burn of the Back, Photographed Twenty Months after the Injury.⁸ The uneven distribution of the keloid over the burned area is characteristic. (Photograph by Signal Corps, United States Army)

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The burns are of the "flash" type, produced by a source of high intensity and brief duration. They are of all degrees of severity and although some may heal speedily with little treatment, this is by no means a general condition. Sequelae and over-all mortality probably will vary with the treatment.

Every effort should be made to evacuate the thermal and traumatic casualties early, and to treat them vigorously, to reduce the incidence of complications from delay.

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NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-EIGHTH ANNIVERSARY

House of Delegates, June 13, 14 and 15, 1949

The House of Delegates convened at Wentworth-by-the-Sea, Newcastle, on June 13, 1949, at 7:45 p.m., with Dr. Francis J. C. Dube, of Center Ossipee, as Speaker.

The following delegates answered the roll call:

The President, *ex-officio*
 The Vice-President, *ex-officio*
 The Secretary-Treasurer, *ex-officio*
 Samuel Feiner, Asbland
 James Jessup, Laconia, alternate for Roger P. Brassard
 W. J. Paul Dye, Wolfeboro
 Francis J. C. Dube, Center Ossipee
 Howard Sawyer
 Albert C. Johnston, Keene
 Walter H. Lacey, Keene
 Marjorie A. Parsons, Colebrook
 William H. Gifford, Colebrook
 Leslie H. Sycamore, Hanover
 Leslie E. McKinlay, North Haverhill
 Reginald K. House, Hanover
 Robert E. Biron, Manchester
 Norman W. Crisp, Nashua
 Harris E. Powers, Manchester
 Richard T. Mulvanity
 James B. Woodman, Franklin
 Francis Brown, Henniker, alternate for Warren H. Butterfield
 William D. Penbale, Concord
 Frederick S. Gray, Portsmouth
 Donald W. Leonard, Exeter
 Fred Fernald, Nottingham
 Edna Walck, Dover
 Albert E. Barcomb, Rochester
 B. Read Lewin, Claremont
 Addison Roe, Newport

The speaker declared a quorum present. The president appointed James Jessup as alternate for Roger P. Brassard of Laconia, Howard Sawyer, as alternate for Speaker Dube and Francis Brown, of Henniker, as alternate for Warren H. Butterfield, of Concord.

On motion duly made and seconded it was voted to omit the reading of the minutes of the previous meeting, because of the publication of the proceedings.

The speaker made the following appointments to the Committee on Credentials, Drs. Samuel Feiner, Harris Powers and Albert E. Barcomb, to the Committee on Officers' Reports, Drs. Donald W. Leonard as Chairman, Edna Walck and Fred Fernald, to the Committee on Communications and Memorials, Drs. Norman W. Crisp, Richard T. Mulvanity and Marjorie A. Parsons, and to the Committee on Nominations, Drs. W. J. Paul Dye (chairman), Samuel Feiner, Reginald K. House, Robert E. Biron and Frederick S. Gray.

The Secretary-Treasurer, Dr. Carleton R. Metcalf, then presented his report as follows:

The total membership on December 31, 1947, was 591, that on December 31, 1948, was as follows:

	PAID	
Belknap County	30	
Carroll County	15	
Cheshire County	2	
Cook County	1	
Grafton County	92	
Hillsborough County	175	
Merrimack County	80	
Rockingham County	64	
Strafford County	38	
Sullivan County	22	
Not in County Society	2	
	590	
	UNPAID	
Life members	29	
	29	
	619	

With a flash burn of average severity the epithelium grows out freely (and indeed beautifully) from normal borders and hair follicles, beneath the unorganized eschar, so that healing is rapid. Yet if

Despite the fact that more and more is being learned about the flash burn, little change in the accepted treatment of burns can be made as yet. It is possible that many of these burns will heal rapidly (if they are not too deep), provided adequate shelter and diet are given the patient

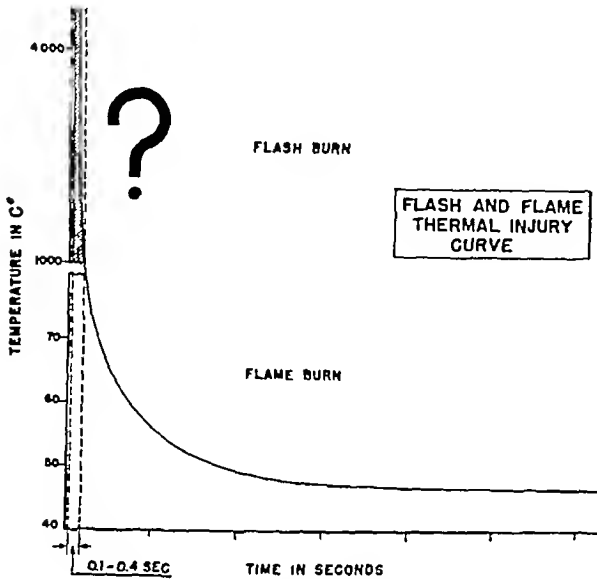


FIGURE 11 Use of the Separation of the Epidermis from the Dermis As an End Point (Henriques and Moritz) to Demonstrate the Relation of Time and Temperature in the Production of Thermal Injury

This graph is a simplified, composite representation of this concept. Studies of thermal effects within the moderate temperature ranges are fairly complete, however, in the extremely high ranges, little has been done. In this zone (shaded in the graph and indicated by the question mark), many factors come into play, which can be ignored in the zones of lower temperature and longer time.

the area is large and the injury deep enough to destroy the epithelium in the crypts and hair follicles, this characteristic demarcation results in delayed repair from lack of epithelial islands.¹⁰



FIGURE 12 Biopsy of Skin Taken Immediately after the Production of a Magnesium Flash Burn on the Side of an Anesthetized Pig

The abrupt lateral demarcation is seen in the epidermis—normal epidermis being to the left and burned to the right. This picture is characteristic of the flash burn.

The prevention of infection—by adequate dressings and antibiotics—will probably pay high dividends in the prevention of morbidity, sequelae and uncalled-for deaths. The entire problem is being studied from several approaches with some promise of a more practical and effective solution.

TABLE 4 Summary of Various Sources Tried¹⁰

SOURCE	DURATION OF FLASH, sec	APPROXIMATE TEMPERATURE, °C	BURN PRODUCED	COMPLICATION
FT14 xenon flash tube	0.002	6,300	None	Unable to focus energy
Exploding wire	0.00001	20,000	None	Unable to focus energy
Thermite	Variable	3,500	None (not used)	too brief blast wave
Gun powder	To 1.0	3,000	None (failure)	Spatter low intensity
Magnesium	0.34	3,500	Severe	Low intensity
Carbon arc	Constant	4,000	Severe	Smoke
				Small area burn

Other factors about these experimental flash burns are their similarity to the ones noted clinically. For instance, severity diminishes as the distance from the source increases. Clothing and heavy creams seem to be adequate protection at reasonable distances from the source. Severity also decreases with the angle of incidence.

CONCLUSION

Thermal and mechanical injuries account for the majority of the casualties from an atomic bomb. From the experiences in Japan, 90 per cent of all persons requiring medical attention in the first week will have burns and 60 to 85 per cent of all patients will be burned.

The burns are of the "flash" type, produced by a source of high intensity and brief duration. They are of all degrees of severity and although some may heal speedily with little treatment, this is by no means a general condition. Sequelae and over-all mortality probably will vary with the treatment.

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The speaker declared a quorum present. The president appointed James Jessup as alternate for Roger P. Brassard, of Laconia, Howard Sawyer, as alternate for Speaker Dube and Francis Brown, of Henniker, as alternate for Warren H. Butterfield, of Concord.

On motion duly made and seconded it was voted to omit the reading of the minutes of the previous meeting, because of the publication of the proceedings.

The speaker made the following appointments to the Committee on Credentials, Drs. Samuel Feiner, Harris Powers and Albert E. Barcomb, to the Committee on Officers' Reports, Drs. Donald W. Leonard as Chairman, Edna Walck and Fred Fernald, to the Committee on Communications and Memorials, Drs. Norman W. Crisp, Richard T. Mulvanity and Marjorie A. Parsons, and to the Committee on Nominations, Drs. W. J. Paul Dye (chairman), Samuel Feiner, Reginald K. House, Robert E. Biron and Frederick S. Gray.

The Secretary-Treasurer, Dr. Carleton R. Metcalf, then presented his report as follows:

The total membership on December 31, 1947, was 591, that on December 31, 1948, was as follows:

	PAID	
Belknap County	30	
Carroll County	15	
Cheshire County	32	
Cook County	31	
Grafton County	92	
Hillsborough County	175	
Merrimack County	80	
Rockingham County	64	
Strafford County	58	
Sullivan County	22	
Not in County Society	2	
	590	
	UNPAID	
Life members	29	
	—	29
		619

FINANCIAL STATEMENT

RECEIPTS

January 1 1948 — balance forward	\$1 170 82
Belknap County	350 00
Carroll County	120 00
Cheshire County	350 00
Cook County	401 00
Grafton County	890 00
Hillsborough County	1 700 00
Merrimack County	796 00
Rockingham County	620 00
Sullivan County	220 00
Strafford County	760 00
Dues collected at annual meeting	40 00
Members not in county society	12 00
Donation to National Physicians Committee	210 00
(Hillsborough County \$7 00 Strafford County \$40 00	
Sullivan County \$22 00 Hillsborough County \$141 00)	
Benevolence Fund	105 00
(Strafford County — 1947 \$10 00 Merrimack County	
\$25 00 Hillsborough County \$45 00 Rockingham County	
\$25 00)	
Balance 1946 meeting	207 94
Refund Cancer Committee	7 69
New England Journal of Medicine subscriptions	7 50
	\$7 967 95

EXPENDITURES

New England Journal of Medicine	
Journals	559 94
Full subscription	7 50
Carlton R. Metcalf (salary)	1 000 00
Printing	302 58
Envelopes, stationery and stamps	26 15
Clerical work	280 85
Telephone and telegraph calls	37 63
Bonds	150 00
Essay contests	100 00
Retaining fee	200 00
Guest speakers (fees)	50 35
Cancer Committee	60 00
Council of New England State Medical Societies	258 70
Benevolence Fund	85 00
(Strafford \$10 Merrimack \$25 Rockingham \$25 Hills	
borough \$25)	
National Physicians Committee	210 00
(Hillsborough \$7 Strafford \$40 Sullivan \$22 Hills	
borough \$141)	
Moving pictures and lantern slides at annual meeting	383 00
Madeline A. May (stenographer at annual meeting)	402 26
Committee lunches	185 97
Hotel Wentworth	201 12
Flowers and registration desk	98 00
Deering G. Smith (expenses as delegate to American Medical	
Association)	320 37
Auditor trustees' books	10 00
Refund on dues	45 00
Press agent	100 00
Women's Auxiliary	100 00
Medals and badges	86 08
	5 294 50
Balance January 1, 1949	2 673 45
	\$7 967 95

In accordance with instructions from the House of Delegates last year the following measures have been carried out \$60 00 was given to the Cancer Committee, \$200 00 was given as a retaining fee to our counsel, Frank J. Sulloway, \$100 00 was contributed for membership in the Council of the New England State Medical Societies.

If we are to continue our membership in the Council, the annual fee of \$100 00 will again be due this year. I have asked Dr. Tuttle, who is reporting on the Council, to take this question up in his report.

I have appeared two or three times before committees of the State Legislature to give my personal opinion on some of the bills that had been entered, but none of the bills have been of medical importance.

Naturally, of course, we have been confronted with the threat of so-called socialized medicine. The House of Delegates met this on a state level by employing the firm of Woodbury and Putnam, of Concord, experts in public relations. Both Mr. Woodbury and Mr. Putnam are here this evening to tell what they have done, how much it has cost and what budget they recommend for the coming twelve months. It will probably be necessary to increase our dues from \$10 00 to \$15 00 a year to educate the people of New Hampshire on the important subject of socialized medicine. We shall, presumably, be concerned with this subject each year for a good many years to come.

The House of Delegates decided to employ Mr. Woodbury and Mr. Putnam at a meeting in Concord last spring, and since that decision was made these two gentlemen have worked in close co-operation with the Public Relations Committee.

I have notified the Veterans Administration that the Society will go along with them on the fee schedule and the agreement for home-town care of veterans with service-connected disabilities. A year ago the House of Delegates voted to do this until further notice.

The committee that arranged this annual meeting has again decided to omit the exhibits, it has continued the plan of having a considerable number of members give brief addresses, it has scheduled the annual dinner for Tuesday evening, and, in general, it has tried to make the meeting of greater interest to a larger group.

The National Physicians Committee has disbanded, and the American Medical Association has taken over the work of educating the public on medical legislation at the national level.

Before the war we used to send delegates to the other state-medical-society meetings in New England, we did not do this during the war on account of the difficulties of travel and have not yet adopted the custom since the war ended. Do you wish now to send delegates to the annual meetings of the other New England states?

Please be sure to read the letter written by Mr. Sulloway, which accompanied your program and which concerned cases of alleged malpractice. It is highly desirable to report to Mr. Sulloway at once any dissatisfaction on the part of any patient.

The little booklet containing the Constitution and By-laws is out of print. It was previously published in 1937. If you wish a new edition of this booklet, the Committee on Constitution and By-laws ought to bring it up to date and report at the meeting of the House of Delegates a year from now.

The expense of the *Transactions* has been going steadily up. It now costs approximately \$3 00 a copy, and it is a question whether very many men read the volume. It would probably be possible to cut the expense of this book if we omitted the various papers that are read at the annual meetings. Do you wish to make any change in the contents of our annual volume?

There are only a few hotels in New Hampshire that can accommodate a convention as large as ours where many who attend wish to stay overnight. Three of these are Hotel Wentworth at Newcastle, Mount Washington Hotel at Bretton Woods and the Mountain View House at Whitefield. The suggestion has been made that we have an annual meeting at Hanover. If this suggestion interests you, it would be well to confer with Dr. Bowler on the subject of food and sleeping quarters.

Dr. Roe stated that \$1600 00 has been advanced to the Woodbury-Putnam Agency to educate the public and inquired what was being done about educating the doctors and also what had happened to the National Physicians Committee.

Mr. Angus B. Woodbury replied that the doctors did not need any education. As far as the public is concerned, this campaign had been what might be called a "quickie." The firm had done the best job that it could, with the time and the money available. He stated that the firm had published news letters, and had tried to report on the progress of the campaign. The different co-ordinating committees, in the separate county societies, should get out the different literature to all the doctors in their areas. During the coming campaign, the firm had plans for getting closer to the doctor.

The Speaker asked Dr. Lull what had happened to the funds that had gone to the National Physicians Committee.

Dr. Lull answered that he had no knowledge of what had happened to the funds, they were not turned over to the American Medical Association.

Dr Harris Powers stated that two checks, dated March 23 and April 21 had been sent to the National Physicians Committee these were in the amount of \$53 00, and both had been returned as soon as the organization had been abandoned

On motion duly made and seconded it was voted to accept the report of the Secretary-Treasurer

On motion duly made and seconded it was voted to dispense with the reading of the reports of the councilors since these will be published in the *Transactions*

President Clarence E Dunbar then spoke as follows

Our hopes for a peaceful year were blasted when we listened to the election returns last year and found that some considered that this meant a mandate from the people to institute socialized medicine The American Medical Association requested that representatives from all the state societies assemble in Chicago on February 12 and Drs Reginald House and Harris Powers were selected to represent New Hampshire Upon their return, they presented the facts of the case before a special meeting of the House of Delegates held in Concord, and the House voted to authorize the Public Relations Committee to engage lay assistance Accordingly, the Angus-Woodhury firm was selected I believe that the results of the campaign organized by this firm fully justify the actions of the House in making this decision

Conferences have been held with representatives of the hospitals dentists, nurses and Blue Cross and Blue Shield, and all have promised full co-operation. In particular, Mr Spaulding, of the New Hampshire-Vermont Hospitalization Service, has given us all possible aid

At the annual meeting of the Council of the New England State Medical Societies, held in Boston on April 20, it appeared that New Hampshire was leading the other states in organizing the campaign

At all times, the attempt has been made to try to emphasize the positive—that is, our campaign is for better medical care rather than against anything As the Public Relations Department of the American Medical Association expresses it

The medical profession has some beams that need strengthening They've been dramatized by recurrent attacks on the doctors A few of the danger spots are excessive fees maldistribution of doctors night and emergency calls that go unanswered rebates insufficient postgraduate education in certain areas, poor press relations, lack of co-operation with laymen and related health groups in planning for medical care neglecting to publicize and implement our 12-point health program and omitting to tell the people about the many progressive activities of the profession on their behalf

I am happy to say that some of the county societies already have done considerable work along these lines

One of the great complaints of the average layman is that the cost of medical care is too high Ordinarily, the patient is satisfied with an explanation that modern medical practice demands more diagnostic procedures and necessarily increased costs for the better services rendered However, unfortunately, we must admit that occasionally some doctors have demanded fees that are out of line with the usual charges in their locality and the patient may have just cause for complaint To remedy this condition in some states, grievance committees have been organized to hear these and other controversial matters that might be brought before them These committees have been very successful wherever organized Therefore, I recommend that the state county and city societies give serious consideration to this plan

To further this idea of better public relations, it is strongly recommended that the Society organize a statewide health conference of doctors laymen and consumers similar to the conference held in Massachusetts last

February A thousand people participated Dr Conlin, of the Massachusetts Medical Society, stated "At no time previously has there been a mass, concentrated attempt here to bring consumers and distributors of health services—the people who are receiving and the people who are doing—together for an exchange of information" Its success was indicated by the Conference's unanimous vote to continue with a similar session a year hence

I have in my possession reports of the preliminary meetings, a list of organizations, representatives invited, by-laws, a complete program and outlines of all panel discussions, which I would gladly turn over to a committee if the House sees fit to organize such a conference

If it does not seem practical to organize such a conference on a state level, it is suggested that city or county societies might well conduct such a meeting on a smaller scale

It must not be assumed, because it now appears that the complete Ewing plan cannot get through this session of the Congress, that we can now sit back and rest We must continue to fight for better medical care and against compulsory health insurance for years to come

To do this means organization, and proper organization costs money Some states are spending several hundred thousand dollars a year in perfecting their plans According to the latest figures available, state dues run from \$10 to \$100, with an average of \$27 County dues run from nothing to \$65, with an average of \$15 I do not doubt that many societies have raised their dues since these figures were compiled

Many states employ full-time executives to assist their secretaries (even Vermont with a smaller membership than ours), and I believe that we should give this plan proper consideration Vermont and New Hampshire have combined successfully in Blue Cross and Blue Shield work, and Dr Bowler suggested that the two states, and possibly Maine also might get together, to organize for the future

To meet our increased responsibilities, the House must give thought to the matter of increasing our dues

In conjunction with the annual meeting of the American Medical Association there is held a conference of presidents and other officers of state medical associations and a conference of county medical society officers New Hampshire should participate more actively in these conferences By the payment of only \$10 00, New Hampshire may be recognized as participating in the Conference of Presidents and I recommend that the Society make this contribution

Many voluntary societies are contributing much to aid the fight against compulsion, and I urge their support by all members In particular, I ask support of the campaign of the American Diabetes Association Also, work has already started on the Crooked Mountain Restoration Center of the New Hampshire Society for Crippled Children and Handicapped Persons, and although some have been critical because of the choice of the site, I believe that all should lend their aid to the project

The American Medical Association is a member of the World Medical Association The United States Committee, Inc. has been organized to support the W M A in its advancement of medicine, health and peace Membership in this committee is open to all, and all members will receive all the publications of the association Membership costs only \$10 00 a year Application blanks may be obtained from Dr Louis H Bauer, secretary, U S Committee Inc., W M A, 2 East 103rd St., New York 29, N Y

It has been many years since our by-laws have been brought up to date, and as there have been some changes I recommend that the House consider their revision and reprinting for distribution to the membership

In conclusion, I wish to thank all the officers and members of the various committees for their splendid work during this past year, and to wish the incoming president a very successful year

On motion duly made and seconded, it was voted to accept the report of the President

The report of the Delegate to the American Medical Association was then presented, as follows

As three sessions of the American Medical Association have been held since the last regular meeting of the Society it is not possible in a report of reasonable length to discuss all that transpired. Only matters believed to be of the greatest interest are mentioned.

At the session last June in Chicago the resolutions on paying physicians engaged in examinations for the armed forces, adopted by this society, were introduced by your delegate and were approved by the House.

A second resolution of this society on single examination acceptable to the armed forces was adopted, with exceptions that did not change the intent of the resolution.

The revised constitution and by-laws were adopted. To conform with them it is recommended that the term of office of the delegate begin on January 1 after the annual meeting at which he is elected. It is believed that no amendment to our constitution and by-laws is necessary to make definite dates for his term of office.

The Council on National Emergency Medical Service requested each state and county society to appoint and organize a similar committee. Our state society has such a committee, but it is urged that every county society also organize one if it has not done so already.

The special Committee on Intern Placements, of which your delegate was a member, approved regulations regarding appointment of interns. In the interest of promoting general practice and making better specialists, it was recommended that all specialty boards require at least one year of rotating internship. It was also recommended that more rotating internships be for two years.

A committee to study conditions of general practice made an extensive report, including in its recommendations that every general hospital be organized so as to give the general practitioners adequate staff privileges and representation.

As it is desirable that some definite procedure be established to choose the outstanding general practitioner in the country each year, it was urged that each county society name a candidate. Each state society would select one general practitioner from this group and submit his name and qualifications to the American Medical Association for the final choice.

It was stated that 32 per cent of the physicians in the country were not members of the American Medical Association. The comparable figure for New Hampshire of 18 per cent is better, but is far too high. Every effort should be made by the county societies to enroll all eligible physicians.

It was voted to urge each state society to defray the cost of the activities of its auxiliary and to pay the annual dues of the national auxiliary, thus making the wife of every member automatically a member of the state and national auxiliaries.

After the Chicago session, the chairman of the Board of Trustees of the American Medical Association appointed your delegate to represent New England on the Association's committee to co-operate with the Red Cross Blood Bank Program. The meetings of this committee have focused attention on the necessity of having available adequate supplies of blood. Our state being very deficient in this respect, it is strongly recommended that a committee be appointed to correct the condition. A statewide blood bank should be sponsored or established at once by our society, either with or without the co-operation of the Red Cross.

At the St. Louis interim session in December your delegate served as a member of the Reference Committee on Reports of Officers. The House of Delegates discussed hospitals practicing medicine, the shortage of physicians in the armed forces and the care of veterans for non-service-connected disabilities. However, the provision of medical care in the American way was the key note of the session, as evidenced by the following:

The House reiterated its approval of nonprofit, voluntary prepayment medical service plans.

At a three-hour hearing resolutions favoring a national enrollment agency and a national insurance company for Blue Cross-Blue Shield Plans were not approved because it was not believed that sufficient factual data had been supplied so that an intelligent decision could be made on this most important subject.

A statement was issued that we are determined to protect and foster the high standards of medical care for the

public, that we are steadfastly opposed to the regimentation and socialization of American medicine, and that we are confident that an intelligent and informed public will join us in our crusade to improve the health and welfare of the American people.

An educational campaign relative to the achievements of American medicine and the dangers of compulsory sickness insurance was begun.

The employment of suitable public-relations counsel to assist in this campaign and the assessment of \$25 on each member of the American Medical Association to finance it were voted.

In January Whitaker and Baxter were employed as public-relations counsel, and they have a vigorous program well underway. At last we have taken the offensive in our battle against socialized medicine.

The session in Atlantic City last week stressed better medical care on a voluntary basis, as evidenced by the approval of the revised twelve-point program for the advancement of medicine and public health, the approval of Associated Medical Care plans that are to become autonomous trade associations, the approval of the development of a national enrollment organization with the understanding that any insurance-company plan must be approved as any other plan, and the recognition of medical care plans operated by lay groups, through the adoption of twenty principles as guides for county and state medical societies in judging whether or not to recommend these plans for approval.

Legislation to enable veterans entitled to medical and hospital benefits for non-service-connected disabilities to obtain these benefits in civilian hospitals of their own choice, under the care of physicians of their own choice, was discussed. A health-insurance plan, the premium to be paid by the Government when the veterans are unable to pay the premiums, was proposed, and after a lengthy discussion the whole matter was referred to the Board of Trustees for study. Resolutions against the governmental participation in business in competition with private enterprise were adopted. Dr. Fishbein was praised for his contributions to the advancement of medical science, but at the same time approval was given to the order that he stop writing and talking about controversial issues. Plans for a new editor and Dr. Fishbein's retirement are being formed. The revised Principles of Medical Ethics were approved. It was brought out that it is unethical to buy appliances, devices or medicines at wholesale and sell them at retail. However, a physician may charge for his services. Every effort should be made to satisfy the needs of the armed forces for physicians from the 8000 educated in whole or in part at Government expense and the 7000 deferred so as to complete their medical education—all of whom have had no military service.

It was suggested that state societies be strengthened where necessary. Your delegate believes that this may be accomplished in our state by the employment of an executive secretary to meet the increasing demands made on our secretary. It is recommended that the president, vice-president and secretary of the Society study this proposal, confer with the officers of the Maine and Vermont medical societies regarding a joint executive secretary and report their conclusions to the House of Delegates.

To strengthen New England's position in the House of Delegates it has been suggested that a common meeting room be obtained and that other delegates be entertained at the meetings. Your delegate asks if New Hampshire's proportionate share of this expense may be included with his other expenses.

The Committee on Hospitals and the Practice of Medicine made a detailed report and recommended the establishment of the same principles governing the proper relations between physicians and hospitals that were adopted by the Massachusetts Medical Society.

It was urged that each state society pass resolutions approving the American Medical Association's Educational campaign. The state and county medical societies should pass resolutions, if they have not already done so, stating their opposition to compulsory health insurance and the socialization of medicine.

Your delegate served during this session as chairman of the Reference Committee on Hygiene and Public Health. He was one of three nominees by the Board of Trustees for membership on the Council on Medical Service but

withdrew in favor of Dr McGoldrick, the present incumbent, who was re-elected

In conclusion, we must not be lulled into a false sense of security because federal health insurance will not be enacted now. The drive for the invasion of the rights of the individual will be continued, and we must oppose it to save not only the medical profession but our country.

Dr Leonard, for the Committee on Officers' Reports, moved that the report of the delegate to the American Medical Association be accepted.

This motion was duly seconded and was carried.

The Committee on Officers' Reports then moved that a committee to be known as the State Blood Bank Committee, be appointed by the President, consisting of three members, whose duties it will be to co-operate with the Blood Bank Committee of the American Medical Association and the American Red Cross, and to draw up plans and initiate action for the establishment of a self-supporting New Hampshire State Blood Bank.

This motion was duly seconded and was carried.

The Committee on Officers' Reports moved that the President be authorized to appoint a committee to obtain specific information regarding the terms, cost of office space, clerical help and other conditions involved in the employment of an executive secretary by the New Hampshire Medical Society, alone or in conjunction with another state medical society. Dr Sycamore and Dr Bowler moved that the motion be amended to include the words "And that the Committee be instructed to report to the House of Delegates at the earliest possible moment, at a special meeting." Dr Leonard accepted the amendment.

The amended motion was duly seconded and was carried.

Dr Leonard, for the Committee on Officers' Reports, then moved that for the promotion of good public relations, the House of Delegates signify that the delegate to the American Medical Association consider his share of the expense of a general meeting room for the New England delegates at the annual convention as a legitimate part of the expenses allotted to the delegate by the Society.

This motion was duly seconded, and after some discussion was carried.

Dr Leonard moved that the New Hampshire Medical Society express full approval of the education campaign being conducted by the American Medical Association through the agency of Whitaker and Baxter.

This motion was duly seconded and was carried.

Dr Leonard stated that the Committee on Amendments to the Constitution and By-Laws had reported that no amendments had been proposed, and the Committee, therefore, had no action to recommend. Dr Leonard moved that the report of the Committee on Amendments to the Constitution and By-Laws be accepted.

This motion was duly seconded and was carried.

Dr Leonard then observed that the Committee on Child Health reported no joint action by the Committee beyond the consideration of plans for the future by the individual members. The Committee, therefore, proposed to defer its formal report to the next annual meeting.

He then called attention to the fact that the minutes of the 1947 meeting of the House of Delegates contained no report of the Committee on Child Health for 1947. In 1946, the Committee reported as follows:

The Committee on Child Health has been relatively inactive. A most important step toward the betterment of the health of children in New Hampshire is the study of child-health services of the American Academy of Pediatrics, which is now in progress. We urge the co-operation of the members of the Society in this study.

Dr Leonard, for the Committee on Officers' Reports, offered an amendment to the present report, to include mention of the recent announcement of the findings and recommendations of the three-year study mentioned in that report of the Committee in 1946. The announcement and a reprint from the *Quarterly Review of Pediatrics*, for May, 1949, had been received by the Chairman. The Academy report indicated that there were only eleven pediatricians in New Hampshire and that three fourths of the private care of children of the nation was in the hands of general practitioners, nearly half of whom had no hospital training in child care, even a fourth of the pediatricians themselves had little hospital training in the medical care and health supervision of children. Three quarters of the nation's practicing pediatricians were in cities of 50,000 or more population — half in communities having medical schools. A third were in Massachusetts, New York and Pennsylvania. The general practitioner, who was principally responsible for protecting the health of children, actually had little time for preventive measures, since only 9 per cent of his time was given for well-child care.

The committee making the study recommended strengthening of basic teaching budgets of medical-school pediatric teaching departments toward a better preparation of medical students, the extension of medical teaching and services to outlying areas, and provision of fellowships for graduate study with hospital training in pediatrics prior to entering practice.

The Committee on Officers' Reports offered this amendment, and moved that the requested deferment of the report of the Committee on Child Health be granted.

This motion was duly seconded and was carried. The report of the Committee on Control of Cancer was presented, as follows:

The annual cancer conference conducted by the Committee held a very successful meeting this year on April 12. The various talks given by the Boston and New Hampshire

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The Committee on Officers' Reports then moved that a committee to be known as the State Blood Bank Committee be appointed by the President, consisting of three members, whose duties it will be to co-operate with the Blood Bank Committee of the American Medical Association and the American Red Cross, and to draw up plans and initiate action for the establishment of a self-supporting New Hampshire State Blood Bank.

This motion was duly seconded and was carried.

The Committee on Officers' Reports moved that the President be authorized to appoint a committee to obtain specific information regarding the terms, cost of office space, clerical help and other conditions involved in the employment of an executive secretary by the New Hampshire Medical Society, alone or in conjunction with another state medical society. Dr Sycamore and Dr Bowler moved that the motion be amended to include the words "And that the Committee be instructed to report to the House of Delegates at the earliest possible moment, at a special meeting." Dr Leonard accepted the amendment.

The amended motion was duly seconded and was carried.

Dr Leonard, for the Committee on Officers' Reports, then moved that for the promotion of good public relations, the House of Delegates signify that the delegate to the American Medical Association consider his share of the expense of a general meeting room for the New England delegates at the annual convention as a legitimate part of the expenses allotted to the delegate by the Society.

This motion was duly seconded, and after some discussion was carried.

Dr Leonard moved that the New Hampshire Medical Society express full approval of the education campaign being conducted by the American Medical Association through the agency of Whitaker and Baxter.

This motion was duly seconded and was carried.

Dr Leonard stated that the Committee on Amendments to the Constitution and By-Laws had reported that no amendments had been proposed, and the Committee, therefore, had no action to recommend. Dr Leonard moved that the report of the Committee on Amendments to the Constitution and By-Laws be accepted.

This motion was duly seconded and was carried.

Dr Leonard then observed that the Committee on Child Health reported no joint action by the Committee beyond the consideration of plans for the future by the individual members. The Committee, therefore, proposed to defer its formal report to the next annual meeting.

He then called attention to the fact that the minutes of the 1947 meeting of the House of Delegates contained no report of the Committee on Child Health for 1947. In 1946, the Committee reported as follows:

The Committee on Child Health has been relatively inactive. A most important step toward the betterment of the health of children in New Hampshire is the study of child-health services of the American Academy of Pediatrics, which is now in progress. We urge the co-operation of the members of the Society in this study.

Dr Leonard, for the Committee on Officers' Reports, offered an amendment to the present report, to include mention of the recent announcement of the findings and recommendations of the three-year study mentioned in that report of the Committee in 1946. The announcement and a reprint from the *Quarterly Review of Pediatrics*, for May, 1949, had been received by the Chairman. The Academy report indicated that there were only eleven pediatricians in New Hampshire and that three fourths of the private care of children of the nation was in the hands of general practitioners, nearly half of whom had no hospital training in child care, even a fourth of the pediatricians themselves had little hospital training in the medical care and health supervision of children. Three quarters of the nation's practicing pediatricians were in cities of 50,000 or more population — half in communities having medical schools. A third were in Massachusetts, New York and Pennsylvania. The general practitioner who was principally responsible for protecting the health of children, actually had little time for preventive measures, since only 9 per cent of his time was given for well-child care.

The committee making the study recommended strengthening of basic teaching budgets of medical-school pediatric teaching departments toward a better preparation of medical students, the extension of medical teaching and services to outlying areas, and provision of fellowships for graduate study with hospital training in pediatrics prior to entering practice.

The Committee on Officers' Reports offered this amendment, and moved that the requested deferment of the report of the Committee on Child Health be granted.

This motion was duly seconded and was carried.

The report of the Committee on Control of Cancer was presented, as follows:

The annual cancer conference conducted by the Committee held a very successful meeting this year on April 12. The various talks given by the Boston and New Hampshire

men were received with interest and discussed freely. The luncheon at noon and all the expenses of this meeting were assumed as usual by the New Hampshire division of the Field Army of the American Cancer Society.

The large group of women in the Field Army have continued their well developed functions, including lay education, distribution of pamphlets and posters, making surgical dressings for indigent patients, transportation of patients to clinics and hospitals, and increasing their large membership. They have supplied reading material for every library in the state and have continued work in high-school cancer education.

There has been a gradual increase of patients attending the state cancer clinics during the past year. On account of the rapid increase in hospitalization expenses during the last two years, the Cancer Commission has found it necessary to apply to the governor and council for extra funds to finish out this fiscal year, and these funds have been allocated without opposition.

As usual, three letters on pertinent cancer subjects have been mailed to each member of the New Hampshire Medical Society. The first one gave information regarding the method of applying to the Cancer Commission for financial aid for medically indigent cancer patients. Immediately after this was issued there was a prompt increase in the number of requests for assistance. The second letter was a discussion of the treatment of carcinoma of the cervix and a warning against attempting an inadequate operation. It stressed the point that operation should be on early cases and should consist of an actual Wertheim operation. The letter stated that a panhysterectomy is not the treatment for cancer of the cervix at any time and is not the accepted form of treatment. It also quoted authorities stating that the choice of treatment of carcinoma of the cervix was still x-ray and radium. The third letter suggested the very important use of every doctor's office as a cancer-detection center and suggested a minimal examination for the patients who come to the doctor for an examination that might detect the presence of cancer. We believe that this is an important service that could be rendered the public by the doctors in New Hampshire.

Owing to the increasing number of members in the New Hampshire Medical Society and to the increased postal rates, your committee spent \$2.75 more than the \$60.00 appropriation, and we request an appropriation of \$70.00 for the next year.

GEORGE C. WILKINS, Chairman
GEORGE F. DWINELL
RALPH E. MILLER
WALTER H. LACEY

Dr. Leonard, for the Committee on Officers' Reports, moved that the annual appropriation for the Committee be increased to \$70.00, and that the entire report be accepted.

This motion was duly seconded and was carried.

The report of the Committee on Industrial Health was then presented as follows:

The Committee has made some gain during the past year in the development and promotion of industrial medicine and health among New Hampshire industries, and it is believed that, with continued effort, New Hampshire will equal, if not exceed, the accomplishments made in our neighboring states and other states in the United States.

A meeting of the Committee was held on February 16, 1949, at the State House, Concord, New Hampshire. Problems discussed and accomplishments of the Committee are included in this report.

Industrial Medical and Nursing Services

During the past year, there were in New Hampshire an average of approximately 89,000 persons engaged in types of industries in which occupational disease and health hazards are known to exist. It is well known that a medical and nursing service program conducted in an industrial plant will decrease substantially occupational disease cases, injury rates, and provide other benefits

that are of economic value to the industry. Table 1 shows the number of workers in New Hampshire who are provided medical or nursing service, or both.

TABLE 1 *Service Provided Workers in New Hampshire*

SERVICE	NO OF WORKERS	WORKERS PROVIDED WITH SERVICE
		%
Medical or nursing, or both	23,150	26
Full time physician at plant	3,000	1
Part time physician	11,850	13
Full time industrial nurse (total)	23,150	26
With direct medical supervision	14,650	16
Without direct medical supervision	8,500	10

The size of the plant necessarily influences the extent of health services provided for employees. Table 2 shows the percentage distribution of workers according to size of plants and the percentage of workers provided medical or nursing service, or both.

TABLE 2 *Distribution of Workers Receiving Service*

SIZE OF PLANT*	PERCENTAGE OF WORKERS ACCORDING TO SIZE OF PLANT	PERCENTAGE OF WORKERS PROVIDED MEDICAL OR NURSING SERVICE OR BOTH
6-250	47.2	Less than 1
250-499	23.7	22
500-1,000	18.9	38
1,001-2,500	5.8	100
2,501 and over	4.1	100

*According to number of workers.

The above data indicate that the larger plants provide medical and nursing services, whereas there are many plants with a working force between 500 and 1000 persons that provide no medical or nursing service for their employees. These plants include shoe, textile, wood products and other industries. Similarly, there is a greater number of plants employing 250 to 500 persons that provide no medical or nursing service for their workers.

Although pre-employment and periodic physical examination of employees is the essential basis for a medical and health program in industry, only 60 per cent of plants providing nursing services also provide for physical examinations of their employees. Table 3 shows the number and percentage of industrial workers who receive the benefits of physical examinations.

TABLE 3 *Workers Receiving Physical Examinations*

TOTAL NO. OF EMPLOYEES PROVIDED MEDICAL OR NURSING SERVICES	TOTAL NO. OF EMPLOYEES PROVIDED WITH PRE-EMPLOYMENT PHYSICAL EXAMINATION	PERCENTAGE OF WORKERS HAVING PHYSICAL EXAMINATIONS
23,150	13,850	60

One plant in New Hampshire employs a full-time physician as medical director, in addition, there are at present 39 full-time industrial nurses who are providing services for 23,150 industrial workers employed in 22 industrial plants in New Hampshire.

Justification for industrial plants to provide medical and nursing facilities for their employees is well established. To mention one example, a survey conducted by the

National Association of Manufacturers concluded that no plant, however small, can afford to be without a health program. The annual net profit to the average plant of 500 employees from the operation of a health program is \$5610. The yearly loss to a company of 500 employees that operates without a health program may be \$39,000. Benefits derived from these services according to this survey included compensation-insurance reduction, lower absenteeism, less labor turnover, reduction in occupational diseases and in accident frequency.

The Committee believes that one of the objections raised by industry to the establishment of medical and nursing programs was the fact that no accurate figures were available concerning the cost and benefits of such services. It was pointed out during Committee discussions that where industrial medical services were provided for employees on a fee basis, industry could not budget for this expense, having no information on the yearly cost, and hence, industrial officials were reluctant to inaugurate medical programs. However, if medical service was on retainer basis, a method of payment that is being used in the majority of the plants throughout the United States, industry would have definite information concerning the cost of the service and would be able to plan and budget for the program. It was further noted in the discussions that this is particularly true with the smaller plants and that some consideration should be given by the physicians in the State to this method of payment. Several members of the Committee indicated that payment for their services was made both ways — namely, on a fee basis or on a retainer basis — and that, as far as they were concerned, either method was satisfactory. However, some physicians are not in a position to know, in all plants, the approximate cost on a yearly basis, and it was pointed out that it might be well for the physician to provide his services for a year on the fee basis, at which time, he would have sufficient information to estimate the approximate cost on a yearly retainer basis.

The Committee realizes that concrete information should be made available for industrial officials relative to the cost of establishing medical dispensaries and operating costs, including fees or retainer salaries for physicians, nurses' salary, equipment, supplies and other expenses. In an attempt to provide this information, the Committee in co-operation with the Department of Health, is now preparing a publication on the benefits and costs of industrial and medical nursing services in industries in New Hampshire. Figures being collected from several plants in the State show the actual costs and benefits derived from medical service programs. Data will be available on initial cost of inaugurating medical and nursing services, operating costs and benefits derived, including decrease in absenteeism, decrease in accident and occupational disease, improvement of employee relations with management and increased production.

It is the belief of the Committee that, if specific information and data are available for industrial officials, they will recognize the value of such services and take steps for their inauguration in the plants.

Medical Services for Small Plants

The Committee has under consideration a program whereby several small plants located near together can combine and operate a central industrial medical dispensary staffed with a full-time nurse and a part-time physician. It has been demonstrated in other sections of the United States that such a program can be successful when several small plants combine their efforts and facilities for the establishment of a medical and nursing dispensary for the use of all plants participating. It is expected that this program will get under way during the coming year, and we shall have more information to report next year.

Preplacement Physical Examinations

The Committee, in co-operation with the Division of Industrial Hygiene, has published a booklet entitled, "Health Evaluation Examinations in Industry." The purpose of this publication is to inform industrial officials of the benefits derived from pre-employment and periodic physical examinations of their employees, and to indicate

to them basic data included in a complete physical examination. In addition, certain screening techniques are given whereby the industrial nurse can evaluate the health status of her applicants for employment as an aid in proper placement of employees in plants where complete physical examinations are not performed by a physician. It is recommended that all suspicious or doubtful cases be sent to a physician for a complete medical examination. It is believed that such screening techniques are better than no medical examination, and that they will demonstrate the value of physical examinations for all employees to industrial officials. Copies of this publication have been mailed to industrial officials, physicians, nurses and other organizations and persons interested in industrial medicine and health.

Chest X-Ray Examination of Industrial Employees

The Committee has worked closely with the New Hampshire Health Department in its program of providing free chest x-ray study for industrial employees. As of June 1, 1949, 15,532 industrial employees in 55 plants had received chest x-ray examinations. The provision of these facilities, through the co-operation of the Health Department and the New Hampshire Tuberculosis Association, is a program that should receive full support from the Society. The Committee strongly endorses this program and urges its continuation.

New Hampshire Industrial Nurses' Association

The New Hampshire Industrial Nurses' Association, in co-operation with the New Hampshire Health Department, has prepared and published a pamphlet entitled "Personnel Policies and Practices for Industrial Nurses in New Hampshire." The Committee endorses the aims and objectives of this organization, and has worked closely with it in the promotion and improvement of industrial nursing in New Hampshire.

Industrial Health Committee, New Hampshire Manufacturers' Association

The Committee has kept the Industrial Health Committee, New Hampshire Manufacturers' Association, informed regarding its activities, and it is planned, in the near future, to have a joint meeting of the two committees to discuss and evaluate programs for the improvement of the medical and nursing services in industry, and for the development of joint activities for the betterment of the health of the industrial workers in New Hampshire.

Information on Toxic Chemical and Other Substances Used in Industry

The Committee believes that information should be prepared, published, and circulated among physicians, nurses and industrial officials relative to the toxic chemicals and substances used in industry. Many of the new materials developed during the war are being used in the plants throughout the State, and it is believed that information about their toxicity, symptoms of poisoning and other information should be made available to give better protection for the industrial workers who are exposed to these substances. Of particular importance are the radioactive isotopes, the increased use of fluoroscopic equipment and x-rays, and the development of methods for the use of beryllium. The Committee has requested the Division of Industrial Hygiene to prepare in mimeographed form pertinent information on such substances for distribution.

Reporting of Occupational Diseases

The passage of the Occupational Disease Compensation Law, two years ago, by the Legislature emphasizes the need for reporting occupational diseases to the Health Department. The Committee believes that, for the fair and just awarding of compensation for occupational disease, all facts relating to the case should be determined and evaluated. It is desired to point out that the Bureau of Labor holds hearings on compensation cases, and that the medical evidence rests largely with the physicians who have seen the case. There should be a definite relation between the patient's exposure to a toxic

substance and some assurance that the quantity to which he was exposed was sufficient to give symptoms of poisoning and that the medical findings definitely relate to the physiologic reaction of the substance in question. It is the belief of the Committee that proper evaluation of all cases can be obtained through the technical assistance of the Division of Industrial Hygiene, which has instruments available to measure and evaluate the degree of exposure and to perform laboratory analyses for the determination of toxic substances present in commercial or other products. For these reasons, the Committee believes that the reporting of occupational diseases to the Health Department is important, so that studies and investigations can be made and methods inaugurated to prevent future cases.

DAVID W. PARKER, M.D., *Chairman*

Dr. Leonard, for the Committee on Officers' Reports, moved that the report of the Committee on Industrial Health be accepted.

This motion was duly seconded and was carried.

The report of the Committee on Maternity and Infancy was then presented, as follows:

STUDY OF MATERNAL DEATHS, STILLBIRTHS AND INFANT DEATHS UNDER ONE YEAR FOR 1948

This is the fifteenth year in which the Committee has conducted an annual study of maternal deaths, infant deaths and stillbirths. Maternal deaths are appraised carefully through the analysis of data from the physicians reporting the deaths. It has been impractical and im-

TABLE 1 *Maternal Deaths by Groups, according to Responsibility for Death*

GROUP	CLASSIFICATION	NO OF CASES
I	Those in which the patient was at fault because of refusal or neglect of prenatal care, self-induced abortion and so forth	4
II	Those in which the obstetrical treatment was inadequate	3
III	Those which were apparently unavoidable	6
IV	Those in which data were insufficient and cause was therefore undetermined	1
Total		14

possible to duplicate this method for infant deaths and stillbirths since the numbers are so great and the Committee's time so limited. However, the Committee compiles a list of these infant deaths by causes as recorded on

TABLE 2 *Causes of Maternal Death*

CAUSE	NO OF DEATHS
Abortion (spontaneous, therapeutic or of unspecified origin) with mention of other infection	1
Ectopic gestation with mention of infection	1
Ectopic gestation without mention of infection	1
Toxemia of pregnancy	1
Hemorrhage of childbirth and puerperium, placenta previa	2
Other and unspecified hemorrhages of childbirth and puerperium	1
Puerperal pyelitis and pyelonephritis	1
Puerperal embolism and sudden death	1
Puerperal eclampsia	2
Puerperal albuminuria and nephritis	2
Laceration, rupture or other trauma of pelvic organs and tissue	1
Total	14

the death certificates, to keep an annual record of chief causes and their variations from year to year. It may be of increased value as the years go on to study trends in the factors contributing to the death of infants and stillbirths. Tables 1-7 show maternal deaths for 1948 by

cause, occurrence (county — urban and rural), groups designating or emphasizing responsibility in the conduct of the case and a list of maternal death rates per 1000

TABLE 3 *Grouping of Causes of Maternal Death*

CAUSE	NO OF DEATHS
Nephritic (toxemia)	6
Rheumatic heart disease	2
Ectopic pregnancy	2
Inversion of uterus	1
Hemorrhages of childbirth	
Placenta previa	2
Undetermined	1
Total	14

live births by years since 1933, as well as infant deaths and stillbirths by cause and sex for 1948.

It should be reported that the method of conducting this study for the calendar year 1948 was done as in the

TABLE 4 *Maternal Deaths, by County, for Urban and Rural Areas*

COUNTY	URBAN	RURAL	TOTAL
Belknap	1	0	1
Carroll	0	0	0
Cheshire	1	0	1
Cook	1	0	1
Grafton	7	0	7
Hillsborough	0	0	0
Merrimack	2	0	2
Rockingham	0	0	0
Strafford	0	0	0
Sullivan	0	0	0
Totals	14	0	14

past. The co-operation of the Department of Health was obtained through the use of personnel in the Divisions of Maternal and Child Health and Vital Statistics. That the Committee may review and study the cases without bias, all information concerning the identity of the physician, hospital and locality is obtained by the Division of Maternal and Child Health, acting for the Committee.

TABLE 5 *Maternal Death Rates per 1,000 Live Births, 1933-1948*

YEAR	RATE
1933	6.3
1934	5.4
1935	6.1
1936	4.8
1937	4.3
1938	3.8
1939	3.1
1940	3.1
1941	1.9
1942	1.7
1943	2.7
1944	2.9
1945	1.8
1946	1.4
1947	1.1
1948*	1.1

*Number of births in 1948: 12,784.

When that division has compiled and prepared data for study, the Committee meets, discusses, appraises and evaluates the case from factual data at hand. It has been necessary in some cases to request additional information on the conduct of the case after a preliminary meeting. All possible data is sought, that the Committee may determine objectively the proper classification of the maternal death. The Committee wishes to reiterate its

position in realizing that the decisions made are not infallible. It hopes, however, that an impersonal discussion from which the report evolves, together with a letter con-

TABLE 6 Deaths under One Year of Age, according to Cause and Sex*

CAUSE	SEX		TOTALS
	MALE	FEMALE	
Whooping cough	1	0	1
Influenza with respiratory complications specified	1	1	2
Encephalitis lethargica	0	1	1
Tumors of unspecified organs	0	1	1
Diseases of thymus gland	1	0	1
Other general diseases	0	1	1
Unspecified anemias	0	1	1
Diseases of spleen	1	0	1
Simple meningitis	2	0	2
Cerebral hemorrhage	1	0	1
Otitis and other diseases of ear	0	1	1
Bronchopneumonia	13	8	21
Lobar pneumonia	2	1	3
Unspecified pneumonia	1	3	4
Diarrhea and enteritis	6	3	9
Intestinal obstruction	1	0	1
Peritonitis	1	0	1
Acute nephritis	0	1	1
Congenital malformations			
Congenital hydrocephalus	6	8	14
Spina bifida and meningocele	1	3	4
Anencephalus	4	4	8
Other congenital malformations of central nervous system	0	1	1
Congenital malformations of heart	10	12	22
Congenital malformations of digestive system	1	1	2
Other and unspecified congenital malformations	12	4	16
Congenital debility	1	1	2
Premature birth	92	57	149
Injury at birth			
Intracranial or spinal hemorrhage	9	8	17
Other intracranial or spinal injuries	1	0	1
Other injuries at birth	6	3	9
Asphyxia, atelectasis	11	6	17
Infection of umbilicus	2	1	3
Other diseases peculiar to first year of life	6	8	14
Automobile accidents	1	0	1
Conflagration	0	1	1
Accidental mechanical suffocation	2	1	3
Accidental injury by fall	1	2	3
Excessive heat	0	1	1
Obstruction suffocation or puncture by ingested objects	3	0	3
Other and unspecified accidents	1	0	1
Sudden death	1	0	1
Ill defined conditions	1	1	2
Unknown or unspecified causes	0	1	1
Totals	207	150	357

*Infant death rate per 1000 live births in 1948 27.9

taining suggestions to the individual physician reporting the case, may be helpful in the conduct of future similar cases.

This report is made possible only through the co-operation of physicians in furnishing as full and descriptive information and facts as possible. Any faulty judgment on the part of the Committee may be due entirely to lack of pertinent information obtained from the physicians.

This year all but one physician returned the data requested. If the Committee is to continue to conduct this study in future years it is essential that physicians respond as promptly as possible and give as full information as possible.

All cases studied are reported through the Division of Vital Statistics of the State Department of Health, where the death certificates are received and filed.

MATERNAL DEATHS

There were 14 maternal deaths in 1948. The number of births in 1948 was 12,784, giving a maternal death rate of 1.1 per 1000 live births. This rate is identical to that recorded for 1947, when the number of maternal deaths was 15 and 13,638 births were reported. The peak in births was apparently reached in 1947 with a slow and slight downward swing this year with 854 fewer births than in the previous year.

The table of the causes of maternal deaths for 1948 reveals a more varied listing of causes than in most years. However, in grouping similar causes together, it is interesting to observe that 6 out of the 14 deaths were due to nephritic conditions or damage to kidney tissue before or during pregnancy or to puerperal toxemias. The line between an out-and-out nephritis aggravated by a pregnancy and a true toxemia of pregnancy is at times difficult

to draw. It was the opinion of the Committee that the treatment given nephritic patients or those showing symptoms of toxemia, early or late in pregnancy, was generally fearful and inadequate. The Committee believes that heroic medical treatment to such patients should be instituted as soon as the signs and symptoms appear. There seems to be, as there has been in past studies, an uncontrollable temptation on the part of some physicians to empty the uterus at all costs and ignore the necessity of treating the patient. The Committee condones the interruption of the pregnancy in toxemias as part of the accepted treatment, and by the most safe and logical means, but it decries the forceful dilatation of the cervix followed by forceps delivery under any circumstances. Due and deliberate consideration should first be given to the degree of prematurity and, above all, to the medical control as far as possible of the condition by the use of magnesium sulfate intravenously alternated with glucose and sedation and when convulsions are imminent, a rapid digitalization. The decision when and how the pregnancy should be terminated is admittedly a very difficult one, and the Committee believes that in all such cases competent consultation should be sought with an obstetrician.

In 2 of the maternal deaths a definite diagnosis of rheumatic heart disease was made before pregnancy. In 1 of these the patient sought no prenatal care and died of hemorrhage and congestive heart failure after a home delivery. This was the only home delivery in this series and one of the very few recorded for several years.

There were 2 ectopic pregnancies. One occurred without warning and in the absence of a history of pregnancy and no external bleeding. The other was undiagnosed before death despite a previously performed dilatation and curettage and a definite history of pregnancy and external bleeding.

Of 3 hemorrhages of childbirth, 2 were placenta previa and 1 was due to a self-induced abortion.

The Committee classifies the causes of death in accordance with the data and facts presented and may, in some cases, differ in the diagnosis from that recorded on the death certificate and as coded according to the International List of Causes of Death by the Division of Vital Statistics. In 1948, however, there was complete agreement and the table, therefore, shows only one listing of these causes.

The Committee further classifies maternal death causes, for purposes of this study, into the four groups shown in Table 1.

Only 1 case was classified as undetermined because of insufficient data. The largest number of cases was classified as unavoidable, with the patient's negligence taking a close second place. The Committee believed that in 3 cases there was definite evidence that the obstetric treatment and conduct of the case were inadequate. It may be of interest to review these cases briefly. Causes listed in this group were 1 ectopic pregnancy, 1 hemorrhage of childbirth (placenta previa), and 1 puerperal eclampsia.

The ectopic pregnancy occurred in a twenty-five-year-old woman who had given a history of having missed a period. Irregular and profuse vaginal bleeding had occurred about two weeks before the final episode, at which time she was admitted to a hospital and had a dilatation and curettage. A diagnosis of possible miscarriage was made. After discharge she continued to have moderate, irregular bleeding. Suddenly, a severe vaginal hemorrhage developed, and because of a confused history, including the imbibing of alcoholic beverages, she was thought to be suffering from acute alcoholism. She became rapidly weaker and when admitted to the hospital again did not respond to treatment and died in apparent shock three hours after admission. A diagnosis of acute alcoholism, with question of shock was made. Autopsy revealed rupture in an ectopic pregnancy and pelvic hemorrhage. The Committee believed that a diagnosis should have been made at the time the dilatation and curettage were performed and again when the vaginal hemorrhage occurred. Any patient who bleeds during the first two months of pregnancy should always arouse a suspicion of an ectopic pregnancy.

The case reported as placenta previa in this group was in a woman who was pregnant for the tenth time. She did not seek prenatal care and claimed to have had a

substance and some assurance that the quantity to which he was exposed was sufficient to give symptoms of poisoning and that the medical findings definitely relate to the physiologic reaction of the substance in question. It is the belief of the Committee that proper evaluation of all cases can be obtained through the technical assistance of the Division of Industrial Hygiene, which has instruments available to measure and evaluate the degree of exposure and to perform laboratory analyses for the determination of toxic substances present in commercial or other products. For these reasons, the Committee believes that the reporting of occupational diseases to the Health Department is important, so that studies and investigations can be made and methods inaugurated to prevent future crises.

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YEAR	RATE
1933	6.3
1934	5.4
1935	6.1
1936	4.8
1937	4.3
1938	3.8
1939	3.1
1940	3.1
1941	1.9
1942	1.7
1943	2.7
1944	2.9
1945	1.8
1946	1.4
1947	1.1
1948*	1.1

*Number of births in 1948, 12,784.

When that division has compiled and prepared data for study, the Committee meets, discusses, appraises and evaluates the case from factual data at hand. It has been necessary in some cases to request additional information on the conduct of the case after a preliminary meeting. All possible data is sought, that the Committee may determine objectively the proper classification of the maternal death. The Committee wishes to reiterate its

department is the availability of a thoroughly trained anesthetist. Physicians should be encouraged to receive special training in this field so that the supply of much needed personnel will be ready to meet the demands.

The Committee believes that cesarean sections should not be performed without competent consultation with a qualified obstetrician.

The Committee wishes to point out that the third stage of labor is the most dangerous of all the stages. When the placenta is expelled great care should be taken that any exertion of pressure always be in the anteroposterior direction. An early Credé maneuver on the uterus should not be done unless it is done during contractions of the uterus and then in the anteroposterior plane. No placenta, it is urged again, should ever be delivered unless the fingers of one hand are between the fundus of the uterus and the symphysis pubis. If these things are observed the Committee believes that inversion of the uterus will be prevented. Although the incidence of inversions is small, the shock and sudden death of the patient developing this condition is so dramatic that a repeat performance would be disastrous so far as the physician is concerned. The Committee observes that inversions of the uterus are included as causes of maternal deaths in most past reports.

The Committee wishes to thank all physicians who reported maternal deaths for their co-operation in furnishing the necessary and detailed facts on each case. Thanks is also extended to hospitals for making records available and preparing copies of such records for use of the Committee. Any recommendations or comments from physicians throughout the State that would assist the Committee in submitting a more helpful report are welcome.

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ROBERT O. BLOOM, M.D., *Chairman*
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This motion was duly seconded and was carried.

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As a result of the Campaign of the American Medical Association, the trustees of the National Physicians' Committee have concluded that their program is no longer necessary, and on April 10 of this year it was voted that the affairs of the Committee should be liquidated. This action brings to a close the activities of this Committee which has been the center of considerable controversy both within and without the profession, and it is undoubtedly best that the public relations of the American Medical Association should be in its own hands.

Schedule of Welfare Cases

In accordance with the instructions of the House of Delegates your committee met with the State Board of Public Welfare to discuss the fee schedule for patients receiving State aid. As a result of the discussion, the Board agreed to request an increased appropriation from the legislature in order to permit an increase in the fee schedule. To the present time, the legislature has taken no action on the budget.

Blue Shield

Growth in membership in the Blue Shield has been much slower in the past year than in the preceding twelve months. Surgical service now covers 175,000 persons

of whom 100,000 are also enrolled in medical service. This decrease in rate of growth is an expected development, since most of the available large employee groups had been enrolled previous to this year, and therefore later increase has been in small units. An important development in making the service more readily available to all citizens of New Hampshire and Vermont has been the vigorous campaign to organize community groups. All communities in New Hampshire now have such groups, and rapid progress is being made in Vermont. Another factor in the decreasing rate of growth has been the cancellation of contracts by some of the larger employers, with the inability of Blue Shield to write coverage outside our own territory as an important factor in these losses. With 20 per cent of the population covered, however, our plan now ranks second in the country in percentage of population enrolled.

Certain tendencies that have developed in the operation of our program require critical scrutiny and necessary corrective measures. A year ago your committee reported that the loss ratio of the surgical service was running in excess of 100 per cent, and made necessary an increase in premium rates. This increase was effective on July 1, 1948, and for the remainder of the year the experience was within reasonable limits. There has been a steady rise in the curve of utilization, however, and the rate at the present time, as indicated by hospital admissions, is at a level about 30 per cent above the expected rate as shown by the averages of the other New England states. It is difficult to determine the cause of this excessive utilization, but the question of abuse of the service by unnecessary use must be considered as one possible contributing factor.

The great majority of the members of the New Hampshire Medical Society have given full support to the Blue Shield program, but a small minority have obviously been guilty either through ignorance or design, of abusing the service for their own advantage. Such actions not only overburden the plan financially and unjustly penalize the co-operating physicians but also adversely affect the reputation of the program in the eyes of the public.

There has also been a generally increased tendency to charge fees in excess of the allowance in the schedule of benefits. Although this schedule was not intended to be a fee schedule, it was the understanding, when the plan was originally instituted, that in the low-income group, fees charged should not exceed the benefit allowed. At present, "low income" is generally considered to be any income up to \$3500 per year per family. For the protection of the policyholder it may be necessary to write a service contract for this group unless full voluntary co-operation can be obtained from the members of the sponsoring societies.

The excessive loss ratio can be met in one of three ways. First, the subscriber rates can be raised to the point necessary to cover the present cost. This step would be unfair to the subscribers until we as doctors are sure that we are all living up to our part of the agreement, and at this particular time, it would have an unfortunate effect from a public relations point of view. Secondly, payments to physicians may be prorated to cover the loss, and for the first time in the history of the plan, the Board of Directors considered this action to be necessary as affecting the May payments. Thirdly, any abuse by the minority must be controlled by the majority.

The action of the Cheshire County Medical Society furnishes an answer to some of these difficulties. In brief, the members have officially voted to accept the benefit allowance as full payment for services to the low-income group, and the staff of the Elliott Hospital in Keene has set up a committee to review all Blue Shield and Blue Cross admissions. The Board of Directors of the Blue Shield instructed its president to request each hospital staff to set up such a committee.

The New Hampshire and Vermont medical societies are the sponsors of our Blue Shield Plan and are responsible for its healthy growth. The promotion of voluntary sickness insurance is the cornerstone of the American Medical Association's educational campaign. It is therefore the obligation of each one of us to do everything in his power to make our own Blue Shield successful.

normal pregnancy until profuse vaginal bleeding occurred near term. She was taken to the hospital, where a transfusion was attempted. She was apparently in labor, but the uterus admitted only two fingers. A forceful manual dilatation was performed, and a stillborn infant delivered by forceps after the delivery of the placenta, which came down first. No rupture of the lower uterine segment was found. The patient died a few hours later. The Committee believed that consultation should have been sought and a more vigorous effort made to administer plasma and whole blood. It was the opinion that the patient might have had a better chance had a cesarean section been done, preceded and accompanied by adequate intravenous therapy with glucose and whole blood. This was especially considered a more desirable approach since the membranes had not ruptured and the cervix was not dilated to any degree.

The puerperal eclampsia reported and classified in Group II was a primipara, forty-three years of age, who had been given prenatal care from the earliest possible time

convulsions before a physician was called, 1 woman, who had had a kidney removed because of tuberculosis, and who had a history of hypertension over many years and became pregnant despite medical counsel to the contrary, died near term of complete failure of the remaining kidney despite every possible intensive medical treatment and delivery of a stillborn child by cesarean section when premature separation of the placenta was diagnosed, another case was in a woman with severe rheumatic heart disease who did not seek prenatal care and refused medical advice concerning pregnancy.

These cases point up the problem of attempting to inform the public of the necessity for adequate and early prenatal care. The Committee believes that physicians should seek and accept all available assistance from private and public agencies concerned with maternal health to the end that women seek a physician's services as early as possible in pregnancy.

In the group of unavoidable deaths there were the following ectopic pregnancy — acute rupture without vaginal bleeding, 1 case, puerperal nephritis with terminal pulmonary edema, 2 cases, inversion of the uterus, 1 case, placenta previa and pulmonary infarct, 1 case, and puerperal embolism and rheumatic heart disease, 1 case.

In the 1948 series of maternal deaths 5 autopsies were performed or recorded. This represents approximately a third of the number of cases and the Committee urges that more post-mortem examinations be performed as the years go on so that more accurate conclusions may be drawn concerning maternal mortality and morbidity.

COMMENTS AND RECOMMENDATIONS

In summary, the Committee attempts to emphasize by way of making recommendations and comments certain principles that may be of value in the deliberation of future conduct of comparable maternity cases. It is noted with gratitude that again almost half the total deaths reported were determined as unavoidable. This means that deaths from maternal causes occur chiefly through accidental or unavoidable circumstances. The decreasing maternal death rate of actually only 1 maternal death for every 1000 live births is indeed encouraging. The Committee would like to think that its efforts over the past fifteen years have contributed to this great decrease by the dissemination of information and the presentation of concrete and specific suggestions concerning accepted practices in obstetrics. It may be that a study of maternal morbidity should be undertaken by someone in accordance with requirements of the American College of Surgeons for hospital standards in obstetrics.

Since there has been evidence that treatment of toxemias and nephritic complications of pregnancy was indefinite or inadequate in this study, the Committee recommends that patients who show even the earliest symptoms or signs of suspected toxemia be seen prenatally at least once a week, or oftener if necessary. It cannot be repeated too often that treatment should be started at the earliest possible time. In toxemias (Grade III), this should be a regime of bed rest, sedation and intravenous injection of magnesium sulfate alternated every two hours with concentrated glucose, the dosage regulated according to the severity of the symptoms and adapted to the individual case. If convulsions develop or are threatened, rapid digitalization should be accomplished. Fluids should be limited early, with attention to a salt-free diet in the early stages. Interruption of the pregnancy should be considered with competent consultation with an obstetrician. The concern should be for planning the safest time and method of delivery weighed against all facts governing the individual case.

The Committee wishes to re-emphasize its continued stand on the practice of forceful manual dilatation of the cervix. There is no indication, in the Committee's opinion, for such a practice under any circumstances.

The Committee believes that all placenta previas in primiparas should be delivered by cesarean section, and that all complete previas, whether in multiparas or primiparas, should be delivered by section.

It should be stressed again that anesthesia is of the utmost importance in obstetrics. The goal of all should be that only well trained anesthetists be used if possible. One of the most important services of a hospital obstetric

TABLE 7 Stillbirths, according to Cause and Sex

CAUSE	No of STILLBIRTHS*			TOTALS
	MALE	FEMALE	UNKNOWN	
<i>Causes determined in fetus, placenta and cord</i>				
Malformations of central nervous system	12	11		23
Malformations of other systems or parts	2	3		5
Unspecified coeogeital malformations	0	3		3
Cord condition without mention of placental state	15	10		25
Placental states without mention of cord condition	25	24		49
Birth injury with mention of disproportion but no mention of abnormality of pelvis	4	2		6
Birth injury with mention of malposition of fetus	1	0		1
Birth injury with mention of abnormality of forces of labor	1	0		1
Infection other than syphilis	0	1		1
Erythroblastosis	1	4		5
<i>Causes and conditions in mother associated with fetal death</i>				
Diabetes mellitus	1	1		2
Chronic diseases of genitourinary system	1	0		1
Other acute diseases and conditions	4	0		4
Toxemia with convulsions during pregnancy or labor (eclampsia)	0	3		3
Other toxemias of pregnancy	5	5		10
Infection (ante or intra partum)	0	1		1
Difficult labor with mention of abnormality of bones of pelvis	2	0		2
Difficult labor with mention of malposition of fetus	0	1		1
Difficult labor with abnormality of forces of labor	1	0		1
<i>Ill defined and unknown causes</i>				
Ill defined	43	40	1	84
Unknown	7	10		17
Totals	125	119	1	245

*Stillbirth rate per 1000 live births in 1948, 192

and had not shown any symptoms or findings suggestive of a toxemia until about two weeks before the time when a planned cesarean section was to be performed. Indications for the section were fairly clear cut because of the woman's age and the possibility of renal failure in the face of the appearance of albumin. During the operation the patient's blood pressure suddenly rose and continued to remain high. Albumin was abundant in the urine. Treatment had consisted of a salt-free diet. No intravenous magnesium sulfate was given, nor was any regime aimed at combating the toxemia followed. Six hours after the cesarean section the patient had convulsions and died. The Committee believed that the patient should have been given earlier treatment for toxemia and vigorous post-operative intravenous therapy. Patients presenting even a suspicion of a toxemia should be seen once a week or oftener to check blood pressure and urine. In this case there was apparently a two-week period before hospitalization during which the patient was not seen.

In the other categories it seems sufficient to comment only on the causes as grouped. They are as follows in Group I, 1 case was a self-induced abortion, about which little could be determined. 1 patient neglected to seek prenatal care, had an uncontrolled diabetes and developed

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The Committee therefore recommends that the House of Delegates urge all members of the New Hampshire Medical Society to give full support and co-operation to Blue Shield, that each county medical society be requested to take action similar to that taken by the Cheshire County Medical Society, that each hospital staff be urged to co-operate fully with Blue Shield by appointing an active review committee, and that each county committee of the educational campaign be instructed to contact each hospital in its county to obtain co-operation in this program.

LESLIE K SYCAMORE, *Chairman*
JOSEPH N FRIBORG, M D
FRANCIS J C DUBE, M D

Dr Leonard, for the Committee on Officers' Reports, moved that the report of the Committee on Medical Economics be accepted with the understanding that this motion, when carried, indicates that the Delegates, as representatives of the component parts of the New Hampshire Medical Society, pledge continued support and co-operation to the Blue Shield.

Dr Johnston stated that the Cheshire County Society operated differently from most of the societies. The members went to Mr Shea, who told them what he liked and what he did not like, and the Society had tried to introduce what it thought was right.

One point that was not stressed too well was the Public Relations Committee. It was really a grievance committee, to iron out these difficulties and be accessible to the public. When there are grievances, this committee should have some authority to take care of them. Furthermore, it should look into the question of unnecessary hospitalization and unnecessary surgery, which undoubtedly is present throughout the State, so that there might be some action to stop such things, in order to bolster Blue Shield and Blue Cross coverage. People, for a small fee, would have a guarantee that their medical care would be taken care of.

Mr Russell S Spaulding, for Blue Cross and Blue Shield, stated that in February, 1948, total benefits per thousand participants were high but that was only one month. In general, the figure averaged out through the year. In January and February, 1948, it came up rapidly. It settled back a little bit seasonably in September and October, and then it went sky-high, way out of sight. Although x-ray services and operating room, medication and laboratory room showed a steady increase, the principal and the notable increase was in room and board. The two possibilities, to account for that increase, were the increased rate of hospital stay and increased utilization. Obviously, the great percentage of increase is because of the increase in cases. The only thing that the increase could be charged to was unemployment. Hospital admissions and unemployment claims closely corresponded. Prior to 1947, they continued on a seasonable up and down level. In 1948 jobs were harder to get, and people were out of work longer. When em-

ployment started down, hospital admissions also started down. But in September and October, 1948, the normal seasonable decline in unemployment leveled off, and hospital admissions immediately started to climb and went way out of sight. It appeared that unemployment and hospital admissions were tied in together and that the current increase was probably due to elective surgery. Mr Spaulding continued with the statement that an increase in rates might be necessary in the near future.

In reply to a question he stated that the increase would probably have to be higher than 10 per cent.

Dr Penhale stated that the subscribers needed surgery and were finding that they could have it done at very little expense to themselves. He believed that the fee schedule would have to be changed, so that Blue Shield would not have to pay so much for that surgery. Perhaps that did not answer the problem of how to lower the hospital costs, but it did answer the problem of Blue Shield.

Dr Sycamore observed that the Trustees of the Blue Shield Plan did not believe that the doctors were responsible for all this excessive utilization. They knew that the great majority of the members of the two medical societies were co-operating fully with the program. A certain small minority were definitely not co-operating, utilizing the service to their own and their patients' advantages. Before the rates to the public are raised the medical profession should be very sure that they are fulfilling their part of the bargain, otherwise, they would be sabotaging the whole program of the American Medical Association and of the New Hampshire Medical Society, admitting to the public that organized medicine cannot meet this challenge.

Secretary Metcalf pointed out that, in the beginning, there was a ruling that if they did not break even, the doctors would take a pro rata break on it. He asked what the delegates would think of paying the doctors less instead of soaking the public more — taking \$70.00 for an appendectomy instead of \$75.00.

Mr Spaulding said that his personal opinion was that Blue Shield could probably struggle along until this trend reverses, as it should sometime. If it happened in a month, there would be no problem. But it might not happen for a year. If Blue Shield could struggle along, by withholding a small percentage from the doctors' payments and not changing the fee schedules and the rates, they could get by with the two commissioners, New Hampshire and Vermont. But that would not help the Blue Cross.

Secretary Metcalf asked if the same thing could not be done with the hospitals.

Mr Spaulding replied that, unfortunately, the hospitals had to have money to run them.

Dr Montgomery asked if it would not obviate much of the difficulty and also take away the

charges of unco-operation if the Society adopted for one year the County Welfare Schedule, which pays the doctors \$50.00 for a major operation and \$10.00 for a minor one. That would cut down the hospital admissions, giving the Blue Shield and Blue Cross a chance to build up.

Dr. Feiner stated that if the fee for a major operation were cut down to \$50.00 Blue Shield patients would be placed in the ranks of the indigent patient. As Mr. Spaulding had pointed out, the fault was not with the doctors — it was with the hospital admissions. Since Blue Shield called for semi-private rooms, was there a breakdown on the admissions, showing whether all hospitals were charging semi-private rates for most of the rooms, he also inquired if there was a breakdown of utilization of laboratory and x-ray services.

Mr. Spaulding replied that the hospitals were being paid their established and published rates. It was possible, of course, that the hospitals were putting the patients in the wards and charging Blue Shield semi-private room rates but he did not believe that any of the hospitals were doing that. He demonstrated that operating room, medication and dressings showed a general increase in utilization, but nothing that matched this peak.

The length of stay in the hospital was decreasing and the number of operations had increased.

Dr. Johnston asked whether comparison with the other New England states showed that New Hampshire patients had more illnesses.

Mr. Spaulding replied that there was no question that there was a great deal more hospitalization in New Hampshire than in the other states.

President Dunbar read the following letter from the Portsmouth Hospital, dated May 18, 1949:

After considerable discussion by the staff last evening, we came to the following conclusions:

1. Doctors on our staff will try to cut down on hospital admissions by doing minor procedures outside.
2. To discourage patients from going to the hospital unless they are really sick.
3. Members of the staff have tried wherever possible, to make the admitting diagnosis conform to the regulations of the Blue Cross.

The hospital had further stated that the doctors had cut down considerably, and that they were watching the outpatient work, because the Blue Cross did not pay for that or for x-ray charges.

Mr. Spaulding read the following list of payments for hospital costs: in January, \$170,000, in February, \$175,000, in March, \$176,000, and in April, \$177,000.

Dr. Dye asked if that were not due to increased hospital costs.

Mr. Spaulding stated that it was for nonsurgical illness. There were many reports of people with colds and the like.

Speaker Dube inquired if Mr. Spaulding had any recommendations to make to the House of Delegates or any suggestions concerning the best means available to solve this problem.

Mr. Spaulding answered that his personal opinion was that the Keene Plan should be effectively tried: let the Committee look the cases over, and let the doctors decide whether anybody is abusing it, and if so, let the doctors take it up with the doctors. The only alternative was an increased rate on Blue Cross, there was no question about that. And it would take some help from the new president or the Committee to convince the Insurance Commissioner that there should be a delay of another month.

Dr. Leonard pointed out that there was a motion that the report of the Committee on Medical Economics be accepted, with the understanding that this motion, when carried, would indicate that the delegates as representatives of the component parts of the New Hampshire Medical Society, pledged continued support and co-operation with the Blue Cross and Blue Shield.

Speaker Dube stated that the motion had been seconded before all the questions had come up. He asked all those in favor of the motion to signify assent by saying "aye." There was a chorus of "ayes," and the motion was carried.

(To be continued)

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35431

PRESENTATION OF CASE

First admission A thirty-six-year-old machinist was admitted to the hospital for diagnosis

Four months before admission the patient had a roentgenogram of his chest taken by a mobile unit at his place of work. Several weeks later he was recalled for further x-ray studies and was subse-



FIGURE 1

quently referred to this hospital after being told that he had an abnormal shadow in the right lung. The patient felt well and was completely free of complaints. There was no history of cough, dyspnea, chest pain or weight loss.

A review of the systems and the past history were noncontributory.

Physical examination revealed a well developed and well nourished man. The chest was clear, and the remaining physical examination was negative. There was no cyanosis or clubbing.

The temperature was 99.0°F, and the pulse and respirations were normal. The blood pressure was 120 systolic, 75 diastolic.

The urine was normal. The blood hemoglobin was 13.3 gm, the white-cell count was 10,300, with 54 per cent neutrophils. A stool specimen gave a negative guaiac reaction.

In the hospital the patient remained free of complaints. A roentgenogram of the chest disclosed a rounded area of increased density, measuring 2 or 3 cm in size, in the lower medial portion of the right lower lobe (Fig. 1). Subsequent studies, including an intravenous pyelogram, barium enema and upper gastrointestinal series were negative. On the sixth day a bronchoscopy was entirely negative.

It was believed that in view of the negative studies the patient should be followed in the Out-patient Clinic. He was discharged on the seventh hospital day.

Second admission (three weeks later) In the interval the patient remained completely asymptomatic, and an additional roentgenogram of the chest during one of his two clinic visits was unchanged. Cytologic examination of the bronchoscopy washings taken the day before discharge from the hospital was subsequently reported as "doubtful," and the patient was therefore readmitted.

Physical examination and laboratory studies were essentially the same as at the previous admission.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. J. GORDON SCANNELL The diagnostic and therapeutic problem of the entirely asymptomatic chest lesion that is the by-product of tuberculosis control is a very real one. The present case is an example, for the decision to explore was, according to the protocol at least, made upon an equivocal basis, namely, a "doubtful" cytologic smear. Once the suspicion of cancer was raised, there was no alternative course but to allay it by surgical exploration if necessary.

When we consider the x-ray films, I think it becomes apparent why there was some hesitancy on the part of the staff in electing to explore this patient, for the lesion is quite consistent with a small incidental inflammatory process that was so hidden away in the voluminous substance of the lungs as to be silent. By the same token, even a small carcinoma, located as centrally as this lesion appears, should have sufficiently encroached upon the bronchial tree to have given rise either to cough and expectoration or to the x-ray picture of segmental atelectasis or localized emphysema.

Before going farther may we see the x-ray films?

DR JAMES J McCORT The round area of increased density is in the posterior basal segment of the right lower lobe. It is smooth in outline and shows no calcification. There is no evidence of segmental collapse or obstructive emphysema in the involved segment. No lymph-node enlargement is apparent in the right peribronchial region. The remaining lung fields are clear, and the heart and vessels are within normal limits. I do not see any evidence of involvement of the bones of the thoracic cage.

DR SCANNELL Am I right in saying that the x-ray picture is not that of a benign tumor of the lung with the exception of adenoma? Chondroma is the most common of these benign lesions, fibroma and hamartoma are not rare and yet these tumors usually have a sharply defined border and are quite round, or at the most somewhat lobulated. Similarly, a bronchiogenic cyst should be either a well defined round or an oval lesion unless its outline was obscured by superimposed infection, which, in turn, should have been reflected in the clinical course of the patient.

The differential diagnosis here lies between some chronic, low-grade infectious process and neoplasm. Of the latter, metastatic tumor is for our purpose excluded by the failure to find a primary source. Of the former, tuberculosis comes to mind first, and secondly some localized nonspecific chronic pneumonitis or residuum thereof for which we have not the slightest indication in the record, not even the smallest red herring. Coccidioidomycosis and histoplasmosis are mentioned in passing. As for tuberculosis, I do not see how we can exclude it even if sputum specimens were negative—a finding not reported in the protocol. In the absence of any statement to the contrary, we can assume that there was no unusual exposure to tuberculosis, and there is certainly no evidence of active infection, but there need be none. This could well represent the parenchymal lesion of a primary infection complex and could therefore quite reasonably be treated expectantly. I cannot make out enlarged satellite hilar nodes.

The manifestly disturbing feature of the case is the "doubtful" report of the cytologic washings taken during an otherwise negative bronchoscopy. I understand that "doubtful" indicates a real degree of suspicion on the part of the interpreter of the slide, and not a synonym for unsatisfactory sampling, poor preservation of cells and so forth, which would call for a diagnosis of "unsatisfactory" and a request for another sample. The examination of bronchial washings has been an effective measure in extending the range of the bronchoscope in making the diagnosis of cancer, particularly if an unequivocal diagnosis of carcinoma cells in the sputum is made. It seems reasonable to suppose that irrigation of the suspected limbs of the bronchial

tree should yield a high percentage of positive diagnoses, although it is my impression that the results in our laboratory have differed little from examinations of fresh sputum carefully obtained and sent straightway to the laboratory.

Except for the suspicious cytologic smear there is little upon which to base a diagnosis of carcinoma. Ordinarily a bronchial lesion of this size will give rise to symptoms of pressure, obstruction or irritation. A truly peripheral tumor will not, and is likely to be discovered in a routine chest film, or, if the tumor has involved a pleural surface and caused pain, a film of a nearby joint to discover the cause of the arthritis is apt to demonstrate mischief in the lung. Therefore, although the number of incidental lesions picked up in chest surveys is great, the number of central bronchiogenic carcinomas must be very small. I am aware that this lesion is not central enough to be within the range of the bronchoscope, and therefore my premise that it is large enough to lead to symptoms may be incorrect.

What of bronchial adenoma? Here, again, the lesions are usually central enough to give rise to symptoms—notably hemoptysis or expectoration. An occasional adenoma may be peripheral, but, if so, it has no business producing even a doubtful smear since these are essentially lesions of the bronchial wall and not the mucous membrane.

One tumor that has aroused great interest recently is alveolar adenomatosis probably a multicentric alveolar-cell carcinoma. Although these lesions are multicentric in development, they may be first seen just as this case was seen, with the first of their lesions established. The relation of this type of carcinoma in man to a similar histologic picture of a virus disease in sheep—jagziekte—leads to interesting speculation concerning the genesis of malignant tumors. I do not believe enough of these cases have been seen to make a cytologic diagnosis on the sputum certain, and therefore "doubtful" is the interpretation I would expect.

We are left, then with three likely diagnostic choices. If we did not have the disturbing cytologic report, my vote would be for tuberculosis. Since we have it, we must consider carcinoma. If the cancer is of the usual variety however, it should give an unequivocal smear. I interpret the "doubtful," therefore, to mean malignant cells that the cytologist had not seen in the lung before or were at least unfamiliar enough to shake his confidence. I will therefore choose alveolar-cell carcinoma as the preoperative diagnosis, meaning by that the initial lesion of pulmonary alveolar adenomatosis.

DR JACOB LERMAN Does Dr Scannell mean diffuse tuberculosis or a tuberculoma?

DR SCANNELL I suppose I mean localized tuberculous infection rather than diffuse tuberculosis. I think this is a localized area of infection.

DR HELEN S PITTMAN We are getting a tremendous number of people referred to the Pulmonary Clinic because of the results of industrial survey studies. This is one of them. We are confused by it and do not know what to do about it. This man came in soon after a patient with a fairly similar finding had been operated on and been found to have bronchiogenic carcinoma. So, we took his lesion seriously from the start and decided that he had to be explored. He was sent to the hospital to

be explored. Very recently, we explored a man with, again, a very similar lesion and no symptoms, and found that he had extensive mediastinal metastases so that resection was not considered advisable. In this case our preoperative diagnosis was a combination of two questions, the same ones that Dr Scannell has brought up: tuberculoma and carcinoma. It seemed that this case would probably be suitable for a lobectomy, even though it proved to be carcinoma, granting no mediastinal involvement or hilar-lymph-node involvement was found. Consequently, we went ahead to determine just what this tumor was anatomically and found, as shown by x-ray studies, that it was in the basal portion of the right lower lobe, and as a biopsy procedure we elected to do a segmental resection of that portion of the lung. When the pathologist who was in the operating room reported his finding, I contented myself with that and did no further operation.



FIGURE 2

be worked up as stated in the record and was discharged at the end of a few days because everything appeared to be normal. He turned up in the Pulmonary Clinic a couple of weeks later. At that time we had this doubtful report from the bronchoscopic washing on the smear of the sputum. Dr Lamar Soutter and I discussed it and decided that we should consider this a bronchiogenic carcinoma until it was proved otherwise. The patient accordingly was sent back to the hospital from the Pulmonary Clinic with that diagnosis.

DR CARROLL MILLER From the surgical point of view I would emphasize the implications and statements already made — that this patient should

CLINICAL DIAGNOSIS

Tuberculoma?
Carcinoma?

DR SCANNELL'S DIAGNOSIS

Pulmonary alveolar adenomatosis, localized

ANATOMICAL DIAGNOSIS

Bronchial adenoma

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY The tumor was very well circumscribed (Fig 2) and proved to be entirely endobronchial. It arose in a small branch of the primary bronchus to the lobe, about 2.5 cm distal to the point of resection — in other words, much farther out in the lung tissue than we commonly see bronchial adenomas, and yet histologically that is what it turned out to be.

There are two fairly well characterized types of bronchial adenoma. In one, the tumor resembles very much the appearance of basal-cell tumor of the skin. In the other type the tumor is very suggestive of the carcinoid tumor seen in the appendix and small bowel. This tumor was of carcinoid type. In the vast majority of the tumor, the cells were very small and uniform, and in the section stained with hematoxylin and eosin, I think it would be impossible to distinguish it from carcinoid of the bowel. In one very small area there was a large, atypical mononucleated cell, which is an unusual finding in adenoma. However, I do not believe it would alter my diagnosis. It might possibly explain the fact that a few atypical cells reached the sputum.

DR SCANNELL Did the cytologist explain the basis of the doubtful report?

DR MALLORY No. I cannot find any further information on that.

DR SCANNELL I wish to emphasize that because it is a constantly recurring problem. We must accept "doubtful" as a real finding. Dr Maier* reported a series of four or five bronchial adenomas beyond the range of the bronchoscope. I believe they are quite uncommon.

DR PITTMAN It was on the basis of the doubtful tumor cells that we sent the patient back into the hospital, even though he had been discharged fairly recently after adequate study.

*Maier H C and Fischer W W. Adenomas arising from small bronchi not visible bronchoscopically. *J Thoracic Surg* 16:392, 98, 1947.

CASE 35432

PRESENTATION OF CASE

A forty-seven-year-old housewife, a para III, gravida V was admitted to the hospital because of dyspnea, ascites and peripheral edema.

The patient had been well until one year before entry, when she noted the onset of shortness of breath on climbing stairs. During the following three months, dyspnea on exertion became progressively more severe, and the patient then noted that her legs and ankles became swollen after prolonged standing. These symptoms became increasingly more marked until eight months prior to admission, when she could no longer climb one flight of stairs or do minor household tasks without becoming very tired. She noticed on waking that the lower portion of her face was swollen and that the swelling of ankles and legs no longer cleared overnight. Slight cyanosis appeared at about this time and persisted. A roentgenogram of the chest taken by her physician had shown an enlarged heart. Six months before admission abdominal swelling occurred, and since that time the patient had been almost completely bed ridden. The patient was seen in the Out Patient Department of this hospital, following which numerous studies were performed. Initially the patient responded to treatment with digitalis, diuretics and other cardiac therapy, however, six weeks before admission symptoms returned, and she seemed to have become refractory to treatment. She did not have orthopnea or hemoptyses.

The past history was significant in that prior to one year before admission the patient had never had any symptoms referable to the chest. The patient's mother had no known illnesses during the pregnancy, and the patient was born following a normal, full-term delivery without cyanosis or other neonatal difficulty. Growth and development progressed normally, and as a child she was well and active without dyspnea or other limitations. The patient had rather frequent attacks of tonsillitis until fourteen years of age, when a tonsillectomy and adenoidectomy were performed. She recalled severe epistaxes during childhood and one episode of abdominal pain and fever at eight or ten years of age, but no other symptoms suggestive

of rheumatic fever. At the age of fourteen a "heart condition" was diagnosed, following which she was told not to exert herself too much. She was asymptomatic, however, and took part in all the usual activities of a girl of her age. Subsequently she had married and during the last seventeen years before admission she had five pregnancies, two of which ended prematurely, the cause was unknown. Through all these pregnancies she had remained symptom-free. The patient recalled that during several of the pregnancies a "heart condition" was again mentioned. One of the physicians stated that there was no murmur but that the heart rate was rapid. There was no history of asthma or other chronic pulmonary disease, pleurisy, hemoptysis or dyspnea, although she had had rather frequent winter colds associated with a dry cough. The patient denied ever having had scarlet fever, diphtheria or influenza.

Physical examination revealed a moderately well developed, thin woman who appeared chronically ill and who was slightly cyanotic but in no acute discomfort. There was no clubbing of the fingers. The veins of the forehead, arms and upper chest were distended, as well as the superficial and deep neck veins, where a deep jugular systolic pulse was present. The chest was clear. The heart was enlarged to the left anterior axillary line, with a diffuse apical pulse. There was a Grade IV harsh systolic murmur best heard at the lower left sternal border and apex in addition to a thrill. The murmur was not transmitted to the neck or back and was poorly transmitted to the left axilla, and was not well heard at the base of the heart. The pulmonic second sound was four times greater than the aortic second sound. There were no diastolic murmurs. The pulse was regular. There was marked ascites and liver dullness extended 3 or 4 cm below the costal margin although the liver edge was not palpable. There was a ++ edema of the legs.

The blood pressure reading on the right arm was 115 systolic, 100 diastolic, and on the left, 110 systolic, 95 diastolic. The temperature and pulse were normal, the respiratory rate was 20.

The urine had a specific gravity of 1.016 and gave a ++ test for albumin. The sediment was normal. The blood hemoglobin was 16.0 gm, and the white-cell count 9400 with 68 per cent neutrophils. The total protein was 5.15 gm per 100 cc, with an albumin of 3.66 gm and a globulin of 1.49 gm. The albumin-globulin ratio was 2.5. The blood sodium was 136.4 milliequiv, the chloride 100 milliequiv per liter. The nonprotein nitrogen was 36 mg per 100 cc and the vital capacity 2.1 liters (63 per cent).

A roentgenogram of the chest showed the lung fields to be clear. The diaphragm particularly on the left, was rather low in position and somewhat

limited in excursion fluoroscopically. The heart shadow was increased in size, the cardiothoracic ratio measuring 16.5 to 28 cm., and the enlargement appeared to be in the region of the ventricles. The main-pulmonary-artery shadow and the hilar vessels were somewhat more prominent than usual, but the peripheral vessels in the lungs were not so prominent as usual. There was no substernal mass. An electrocardiogram showed a probably normal rhythm at a rate of 80. No definite P waves were made out. There was moderate right-axis deviation, the T waves were low and upright in Lead 1 and 3, upright in Lead 2, essentially flat in Lead VL and upright in VF. The R waves were high in Lead V₁ and V₄, and the T waves were diphasic in Lead V₂ and upright in Lead V₄ and V₆. This reading showed no significant change over a record taken about two months earlier, except that the P waves were now not clearly present. Five days later another electrocardiogram showed a regular rhythm at a rate of 95 with absent P waves. The special auricular leads also failed to reveal definite P waves. The T waves were low in Lead 1 and diphasic in Lead 2 and 3. The chest leads showed upward deflection in V₂ and downward deflection in V₄ and V₆.

On the sixth hospital day an abdominal paracentesis was performed, with the removal of 3900 cc of slightly cloudy, straw-colored fluid. The specific gravity was 1.010, and the protein 2.20 mg per 100 cc, with 314 red cells and 89 white cells per cubic millimeter. A culture was subsequently reported as showing no growth.

Repeated vital-capacity studies ranged from 60 per cent to 66 per cent. The sedimentation rate was 1 mm in sixty minutes and a prothrombin time 19 seconds (normal, 15 seconds), or 63 per cent. There was little change in the patient's course except for a short period of weakness at which time the serum sodium was found to be 121.7 milliequiv and the chloride 96 milliequiv per liter. This deficiency was corrected by the addition of 10 gm of salt to her diet, following which the patient felt somewhat better. Another electrocardiogram taken on the twenty-sixth hospital day showed no significant changes from the previous readings except for the presence of definite P waves. Several days before discharge the patient complained of tenderness in the legs. Examination, however, was negative for thrombophlebitis. An examination of the chest one day before discharge showed little change in findings. The heart was much as before, with the apical impulse at the left anterior axillary line. There was a slight thrill palpable at the apex and also over the second and third left intercostal spaces.

A Grade III systolic murmur was loudest between the apex and lower left sternal border. The pulmonary second sound was much accentuated, and there was a loud third heart sound along the left sternal border and at the apex, now followed by a questionable slight diastolic rumble.

Since the patient's morale was low and she wanted to go home and since it was believed that little more could be done for her in the hospital, she was discharged on a cardiac regime on the thirty-fourth hospital day.

Three days after discharge she suddenly died at home.

DIFFERENTIAL DIAGNOSIS

DR EDWARD F. BLAND: This patient had been remarkably well until the last year of her life, and the history gives us various but vague information concerning the background for her final decline and death. There are two features that are definite—namely, extreme pulmonary hypertension and subsequent heart failure. As is often true under these circumstances, she went inexorably downhill and died of pure right-sided failure, with clear lungs. She had never had pulmonary edema or hemoptysis.

There are several likely possibilities to explain this clinical picture, but at this point we need help from the X-Ray Department. I have not seen the films, and they may influence considerably the direction of the discussion. What we would like to know, Dr McCort, is the size and shape of the heart, the degree and type of pulsation of the hilar vessels, the character of the lung tissue beyond as to vascularity, and whether or not there is evidence of pulmonary infarction—either old or recent.

DR JAMES J. MCCORT: Examination of the chest shows marked enlargement of the heart to the left side of the chest. There is fullness anteriorly suggesting that the enlargement is mainly in the region of the right ventricle. There is also widening of the pulmonary artery, seen in the right anterior oblique film and enlargement of the right branch of the pulmonary artery. We do not see the left branch well. A paucity of the vascular markings in the peripheral lung fields is noted. There is no evidence of scars from previous infarction. Slight blunting of the right costophrenic sinus is present. We have no information of the character of the pulsation of the right pulmonary artery.

DR BLAND: Do you see any linear scars in the lung parenchyma? Can you say that the auricles are enlarged?

DR MCCORT: I do not believe they are enlarged. There is no posterior or lateral displacement of the barium-filled esophagus.

DR. BLAND Is the aorta normal, is it too small or too big?

DR. MCCORT It is within normal limits I should say.

DR. BLAND The heart is not quite as large as I expected to find it. The pulmonary arteries are moderately enlarged, not huge. The aorta does not appear unusually small. Huge pulmonary trunks and a small aorta would suggest interauricular defect, but that seems unlikely in this patient. We can be reasonably sure however that she had a serious obstruction to the pulmonary circulation. Can we be certain that she did not have rheumatic heart disease and mitral stenosis as a background for this pulmonary hypertension? I do not think so, for several reasons. The history is neither helpful nor the reverse because many people have no rheumatic history and yet develop mitral stenosis of high degree.

The physical signs do not suggest mitral-valve disease, and furthermore the heart rhythm remained normal throughout the twelve months of failure. Most patients under these circumstances would develop auricular fibrillation if mitral stenosis were present. And, finally, with back pressure from mitral stenosis, the lungs suffer. In this patient there is no history or x-ray evidence of lung congestion. Therefore, I do not believe rheumatic heart disease played any part in this picture.

Next we have to consider some congenital lesion that might lead to this situation in the pulmonary circuit. If we take the physical signs as described — the loud systolic murmur and the thrill near the lower sternum — the commonest cause on a congenital basis would be interventricular septal defect. In this condition, however, signs are usually characteristic and are present throughout a person's life, at least from early childhood. If present, such a lesion is not likely to escape comment during three pregnancies. So I am willing to throw out interventricular septal defect.

What else could cause this murmur and thrill? Congenital stenosis of the pulmonary valve might be responsible, but this patient lived too long without symptoms, and the degree of right-axis deviation in the electrocardiogram was hardly extreme enough to warrant serious discussion of this possibility.

How about interauricular septal defect complicating the situation? It would be most unusual to have a murmur and a thrill of this degree from auricular septal defect, and murmurs that exist are related to the tremendous amount of blood flowing through the pulmonary circuit with a relative pulmonary stenosis. So I shall have to put aside for the moment the systolic murmur and

thrill because I cannot logically account for them other than on the basis of pulmonary-artery dilatation.

We have still left unexplained the obstruction in the pulmonary circuit. There are two likely possibilities. First, embolization of the lung can do this, and the cardiac difficulty need not come at the time of embolization. Such cases have been recorded and we have had one here in a patient who following pregnancy had widespread embolization of the lung, presumably from amniotic material. She succumbed four years later from right-sided heart failure under circumstances somewhat similar to those in the case under discussion. Another possibility is embolization of the lung from clinically undetectable thrombophlebitis. There is nothing in the history to point in this direction although terminally there was slight tenderness in the legs. We would like in this connection a clue from the history such as spells of breathlessness in the past, or perhaps pleurisy or hemoptysis — although none of these are essential. Hence, I do not find suggestive evidence for embolization of the lungs as a cause of the ultimate right-sided failure in this case. Secondly, and finally by exclusion we are left with primary endarteritis of the pulmonary arterioles. I know of no way short of lung biopsy to establish this diagnosis clinically, although cardiac catheterization is helpful in puzzling cases. The derangement here, as with widespread embolization of the lung, is pulmonary ischemia. These patients usually are dyspneic before they become cyanotic. In fact, the degree of cyanosis may vary from a barely detectable degree of dusiness to the extremely black appearance of the cardiac patients first described by Auerza. But once right-sided heart failure appears their course is progressively and unremittingly downhill.

Therefore, in summary, it is clear that this patient had a serious obstruction to the pulmonary arterial supply to the lungs sufficient to produce right-sided heart failure. I do not believe mitral stenosis or the Lutembacher combination had any part in this picture, nor is there convincing evidence for a congenital defect. I am left with either widespread embolism of the lungs or a primary pulmonary arteritis as the most likely cause — I prefer the latter.

DR. MCCORT The X-Ray Department suggested the possibility of massive thrombosis of the pulmonary artery to account for the dilated main pulmonary artery and relative avascularity peripheral to the major branches of the pulmonary artery.

DR BLAND The X-Ray Department has become very expert in spotting an obstructing thrombus in a main pulmonary trunk. They have repeatedly—well, perhaps twice—pointed them out to us, and they have been correct. In this x-ray film two main vessels can be seen, one stops abruptly with avascular lung beyond, and the other does not. This is suggestive of thrombosis locally. Perhaps there is one here. But it would be difficult to assume that such an event occurred a year before the patient died and was the explanation for the total illness. It may have been a later complication. It is an interesting speculation, but I do not think a large local thrombus existed here.

DR HOWARD B SPRAGUE I think I recognize this patient as being one over whom we agonized considerably from the standpoint of diagnosis for several months and arrived at about the same conclusion that Dr Bland has, by a method of exclusion. When she was presented at cardiac grand rounds, the question of the left main pulmonary artery came up, and it was reported as being not visible. Later, after fluoroscopy, a pulmonary artery was seen on the left side.

DR BLAND It is hard to see, is it not?

DR McCORT Yes it is.

DR BLAND Because it is obscured by the heart? What did you think she had, Dr Sprague?

DR SPRAGUE We came to the conclusion that cor pulmonale was the most likely diagnosis. I would like to say once more that the rule now seems to be when in doubt, say cor pulmonale. That opinion could well be spread through the country, I think, because it is not too well recognized. In the last case that I saw, in North Carolina, the patient had a tremendous main pulmonary artery and clear lungs—no one made the diagnosis.

DR DONALD S KING What do you mean by cor pulmonale?

DR SPRAGUE I mean primary endarteritis.

DR BLAND It is also worth emphasizing that patients with cor pulmonale rarely fibrillate, in contrast to those with rheumatic heart disease.

CLINICAL DIAGNOSIS

Cor pulmonale

DR BLAND'S DIAGNOSES

Primary pulmonary endarteritis

Embolization of lungs?

Cor pulmonale, with right-sided heart failure

ANATOMICAL DIAGNOSES

Pulmonary emboli, multiple, recent and old, with recanalization

Cor pulmonale

Hydrothorax

Ascites

Peripheral edema

Chronic passive congestion of liver

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY This patient was found at autopsy to have an enlarged heart, the enlargement being almost entirely confined to the right ventricle. The right ventricular wall measured 7 mm in thickness, with a dilated pulmonary conus. This photograph is from the heart and shows the right ventricle with tremendous thickening of the columnae carneae and considerable thickening of the ventricular wall itself (Fig 1). The left ventricle was of normal size. The main branches of the pulmonary artery contained some adherent thrombi or emboli, which showed traces of organization that looked as if they had been present for a week, possibly longer, but certainly not long enough to explain the enlargement of the right side of the heart. When the pulmonary artery was opened further, it was found that, although the main pulmonary artery and its primary branches were free from atheroma, the secondary and tertiary branches had numerous atheromatous plaques. At the next smaller division a point was suddenly reached where the scissors could no longer open the vessels, and it was evident that perhaps the fourth-division vessels were uniformly, almost completely, occluded by fibrous bands that were clearly the result of old organized, recanalized emboli. The case is almost identical with one that Dr Castleman and Dr Bland reported* a short time ago. The microscopical pictures from their case could be superimposed upon pictures from this case. Microscopically small pulmonary-artery branches showed athero-

*Castleman B and Bland E F. Organized emboli of tertiary pulmonary arteries: unusual case of cor pulmonale. *Arch Pathol.* 42:581-589, 1947.

matous plaques, and farther out in the vessels one came upon a point where there were thrombotic plugs and the lumen of the arteries had been divided into five or six small lumens (Fig 2)

DR GORDON MYERS Does Dr Bland think that the systolic murmur and thrill could have been caused by tricuspid regurgitation?

DR BLAND Thrills usually mean stenosis rather than regurgitation, either real or relative. I favor

to have been of the same size and uniformly scattered throughout both lungs, so that embolization must have been a major episode but we could not clearly identify it from the history. We were sus-



FIGURE 1

dilatation of the pulmonary artery immediately beyond the orifice as the most likely explanation.

DR MYERS The thrill was low, between the apex and the left sternal border.

DR MALLORY The tricuspid valve measured 14 cm in circumference. The pulmonary valve was normal in circumference, 8 cm.

DR BLAND I still favor the pulmonary orifice as the origin of the murmur and thrill. In the case Dr Mallory referred to, all the emboli appeared



FIGURE 2

picious of amniotic material at the time of her last pregnancy.

DR BENJAMIN CASTLEMAN Amniotic emboli are much smaller and get out even farther in the pulmonary circuit.

DR BLAND What is your explanation in today's case, Dr Castleman?

DR CASTLEMAN Multiple emboli, probably from the pelvic or deep leg veins.

DR MALLORY The pelvic veins were examined carefully, and no evidence of thrombus was found. The deep leg veins were not examined. The pulmonary vessels at the point of occlusion measured around 3 mm in diameter.

DR JAMES A. CURRENS The presence of pulsation in the jugular vessels might be in favor of tricuspid insufficiency.

DR BLAND Yes.

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BOOMERANG

THE executive branch of the federal Government has given the appearance of getting down to business in a rather shocking manner in its intention to dictate the conditions under which medicine shall be practiced in this democracy. As long ago as February a United Press dispatch from Washington announced plans of the Government "to crack down on alleged antitrust practices of 'several' state medical associations," with the prediction that the action might come soon after President Truman sent to Congress his compulsory national health insurance program.

It would be unworthy of the dignity of American medicine to make capital of the publicized fact that also in February, during the session of the Board of Trustees of the American Medical Association, the Board room was broken into at night and the records of the Board and the brief cases of the trustees were thoroughly searched.

In August the secretary of the American Medical Association received the following letter, emanating from the Department of Justice:

Dear Sir:

In connection with an investigation by this Department of alleged violations of the federal antitrust laws in the medical field, it is requested that you make available for examination by the bearer, an agent of the Federal Bureau of Investigation, such of your files as he may request.

Your co-operation in this investigation will be very much appreciated.

Sincerely yours,

HERBERT A. BERGSON

Assistant Attorney General

September was an active month for the Department of Justice, for during that period of thirty days investigations of the following organizations were launched: American Medical Association, New York State Medical Society, Utah State Medical Association, Washington State Medical Society, Arkansas State Medical Society, Oklahoma State Medical Association, Michigan Medical Service (a Blue Shield prepaid medical-care plan), Arkansas Blue Cross-Blue Shield Medical Care Plan, Los Angeles County Medical Society, Beckham County Medical Society (Oklahoma), Wayne County Medical Society (Michigan), Nassau County Medical Society (New York), Queens County Medical Society (New York), New York County Medical Society, Harris County Medical Society (Texas), and King County Medical Society (Washington).

This is the September list only, during recent months a number of other medical societies also have been asked to open their records to investigation by Antitrust Division agents.

It is, on the whole, better to believe that the current activities of the Department of Justice are purely fortuitous, that they have no connection with the Government's proposed excursion into socialized medicine or the activities of the medical profession in opposing such compulsion. Under the circumstances it is exceedingly unfortunate that the Department of Justice should have chosen this particular time for its investigations. In so doing it lays the Government open to the suspicion of using methods that follow a pattern familiar in certain other countries but are still repugnant in its own.

Astute public officials are hardly likely to employ tactics that may recoil upon themselves.

POSTGRADUATE ASSEMBLY

THE Central Committee in charge of the New England Postgraduate Assembly announces that the eighth annual meeting will be held on November 9, 10 and 11 at the Copley Plaza Hotel, Boston. As usual an interesting and instructive program has been arranged, and as usual an impressive attendance of physicians from the six New England states is expected. Four papers will be presented on each of the three mornings, and six on each afternoon of the first two days. A jamboree — defined by Webster as (1) a noisy carousal or merrymaking and (2) an international or intersectional gathering of boy scouts — will be held on the evening of November 9. As doctors and their wives are urged to participate, the first definition is assumed to be the correct one. Since lusty joy should not be entirely unrestrained, however, in the land of the Puritans, the carousing will be preceded by a short lecture to put the merry-makers in a properly subdued frame of mind.

A feature of the Assembly will be the introduction of television programs in addition to the announced speakers on the mornings of November 10 and 11. These programs, arranged through the generosity of E. R. Squibb and Company, will emanate from the New England Medical Center, drawn by lot from among the various Boston hospitals. Part of the first morning's program will be presented by the staff of the Massachusetts Infantile Paralysis Clinic of the Children's Hospital.

Fifty-six commercial exhibits will occupy the usual booths.

The medical organizations of America have today much of their interest directed toward politics and public relations. Except for these two urgent demands the accent has always been and always should be on mutual improvement and the postgraduate education of physicians. It is one of the important and perpetual reasons for the existence of medical societies.

The New England Postgraduate Assembly is a thoroughly praiseworthy co-operative undertaking of a sectional group of societies. To say that it supplements such activities as the postgraduate lecture course offered each spring by the Massachu-

setts Medical Society to all physicians in the Commonwealth, and the program of postdoctorate medical education for practicing Connecticut physicians currently in operation under the sponsorship of the Yale University School of Medicine and the Connecticut State Medical Society is not enough.

The Postgraduate Assembly in its own right, with its outstanding list of speakers and the other features that it offers takes high rank among such gatherings.

DR ALAN R. MORITZ

RECENTLY, a signal tribute was paid to a distinguished leader in legal medicine. On the occasion of his departure from Massachusetts, Dr. Alan R. Moritz, formerly head of the Department of Legal Medicine at Harvard Medical School and pathologist to the Commonwealth, was honored by a bronze plaque, which was presented with a sum of money to Harvard Medical School in commemoration of Dr. Moritz's ten years of service. In addition he received from his associates in the Massachusetts Medico-Legal Society a scroll in recognition of his achievements in his field.

The *Journal* joins his confreres in wishing Dr. Moritz the best of fortune in his new duties as professor of pathology and director of the Institute of Pathology at Western Reserve University. Regret that the Commonwealth is losing an outstanding figure in legal medicine is tempered only by the conviction that further accomplishments are in store.

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

THE *Journal* congratulates the National Gastroenterological Association and its president, Dr. William Reid Morrison, on the fourteenth annual convention of the Association that has just come to a close in Boston.

Many prominent speakers were on the three-day program, they included, in addition to leading American physicians and surgeons, the Rt. Hon. the Lord Alfred Webb-Johnson, president of the Royal College of Surgeons of London, the subject of whose paper was "Experientia Docet." Lord

Webb-Johnson spoke again at the annual banquet, and is addressing the Postgraduate Course in Gastrointestinal Surgery that follows immediately on the meeting of the Association, on the subject "Some Surgical Adventures"

The Most Reverend Richard J. Cushing, D.D., archbishop of Boston, and James H. Rand, Jr., president and chairman of the board of Remington Rand, Inc., were the other dinner speakers. For the first time in Boston a program of abdominal surgery was presented over television.

Mr. Lacoupey states that, as yet, therapeutics do not teach how to arrest the progress of pulmonary tubercularization, he thinks that he has supplied the desideratum. He has administered, in a multitude of cases, the pharmaceutical preparation pommade mercurielle (mercurial ointment), in pills, a dose from five to forty centigrammes daily, half in the morning, half in the evening. Under this treatment the morbid phenomena soon lessened, and then ceased altogether.

Boston M & S J, October 24, 1849

MASSACHUSETTS MEDICAL SOCIETY



DEATHS

BURBECK — Edward K. Burbeck, M.D., of Marblehead, died on July 1. He was in his seventieth year.

Dr. Burbeck received his degree from Johns Hopkins University School of Medicine in 1907. He was affiliated with the Mary A. Alley Emergency Hospital and was a fellow of the American Medical Association.

His widow survives.

GREENE — Ransom A. Greene, M.D., of Wayland, died on October 4. He was in his sixty-ninth year.

Dr. Greene received his degree from Baltimore Medical College in 1902. He was superintendent of the Walter E. Fernald State School in Waverley and was formerly superintendent of the Taunton State Hospital. He was a member of the American Psychiatric Association and New England Society of Psychiatry and a fellow of the American Medical Association.

His widow, a son and two grandchildren survive.

MISCELLANY

FORMATION OF MASSACHUSETTS HEART ASSOCIATION AND NEW ENGLAND CARDIOVASCULAR SOCIETY

At a meeting of the members of the New England Heart Association held on September 19, 1949, the name of the New England Heart Association was changed to the Massachusetts Heart Association. The present officers and Executive Committee officers will continue until the annual meeting in the spring. In addition, steps were taken to form the New England Cardiovascular Society.

The purpose of this change in name to the Massachusetts Heart Association is to promote greater efficiency of operation in the work of the organization as an affiliate of the American Heart Association, in the development and implementation of a program and in fund-raising activities. Similar state heart associations have been formed in Maine, New Hampshire, Connecticut and Rhode Island, and it is expected that Vermont will soon have its organization. Membership in the New England Heart Association will automatically be transferred to the Massachusetts Heart Association unless a member desires to be transferred to another state heart association.

To avoid too much centralization and yet to prevent diversion into too small and ineffective units, it is planned to organize the State into regional areas, to be known as chapters. Already Worcester County has been so organized, and the other divisions will be Western Massachusetts, North Shore and Merrimac Valley, Southeastern Massachusetts and Greater Boston. Within these areas heart committees will be formed to serve smaller areas.

Each area chapter and committee will be organized with lay and professional representation. The Board of Directors of the Massachusetts Heart Association will provide representation both lay and medical from each of the five area chapters.

The New England Heart Association has been in operation for some twenty-eight years, and its principal function has been to provide a meeting place for physicians throughout New England who wish to report and discuss new work in cardiovascular research. The Executive Committee of the New England Heart Association believes that this function is valuable and should be continued and has recommended that the New England Cardiovascular Society be formed to provide this meeting place for physicians throughout New England interested in cardiovascular disease. The membership will consist of physicians and other persons professionally concerned with cardiovascular research or program development. All present physician members of the New England Heart Association are eligible for election to the New England Cardiovascular Society. There will be no dues in this Association. Members of other New England state heart associations affiliated with the American Heart Association may be elected to membership.

The New England Cardiovascular Society will conduct the hospital meetings, print the *Proceedings* and, in general, represent purely professional interests in this field. The expenses of the Cardiovascular Society will be borne by the Massachusetts Heart Association as part of its function to advance the standards of professional practice and knowledge in the cardiovascular diseases.

The following important committee appointments have been made by the Massachusetts Heart Association:

Research Allocations Committee

C. Sidney Burwell, M.D., *Chairman*
Robert E. Gross, M.D.
Samuel H. Proger, M.D.
Robert W. Wilkins, M.D.
Burton E. Hamilton, M.D.

Boston Chest X-Ray Program for the Study of the Screening of Cardiac Patients

Benedict F. Massell, M.D., *Chairman*
C. Sidney Burwell, M.D.
David D. Rutstein, M.D.

Rheumatic Fever Service Committee

George P. Sturgis, M.D., *Chairman*

Committee for Home Care of the Ambulatory Cardiac

Paul M. Zoll, M.D., *Chairman*
Andrew W. Contratto, M.D.
A. F. Foster, M.D.
Sylvester McGinn, M.D.
Elizabeth Howland, R.N.

Committee on Professional Education

Eugene C. Eppinger, M.D., *Acting Chairman*

Committee for Free Penicillin

Edward F. Bland, M.D., *Chairman*
Maxwell Finland, M.D.
Samuel A. Levine, M.D.
Edwin O. Wheeler, M.D.

Committee on Rehabilitation

Howard B. Sprague, M.D., *Chairman*

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Bone Marrow Biopsy. Haematology in the light of sternal puncture. By S J Leitner, M D, reader in internal medicine University of Berne (Switzerland), and deputy medical superintendent, Sanatorium for Tuberculosis Herligenschwendli, Berne. English translation revised and edited by C J C Britton M D, Ch B, DPH, consulting haematologist to the Prince of Wales's General Hospital, Tottenham, London, and Queen Mary's Hospital, Roehampton and E Neumarck M B, B S (Lond), M R C S, L R C P, lecturer in pathology, St Mary's Hospital Medical School London 8°, cloth 433 pp, with 194 illustrations and 7 color plates. New York: Grune and Stratton, 1949. \$8.50.

Dr Leitner first published his researches in the *Folia Haematologica* in 1941. This material was thoroughly revised and published in the German edition, from which this translation into English has been made. The monograph is intended primarily for clinical use but necessarily contains some technical material. The work is based on investigations carried out at the medical clinic of the University of Berne, where more than 2700 sternal punctures were made on more than 920 patients. The author is convinced that bone-marrow biopsy is of immense practical value in the diagnosis of blood disorders and many other diseases. The larger part of the text is devoted to disorders of the blood, but there are chapters on tumors, liver disease, endocrine disorders and the effects of radium and x-rays on bone marrow. The concluding chapters discuss the metabolism of bone marrow and blood cells, the defense reaction of marrow cells and tissue culture of marrow cells. Extensive bibliographies are appended to the various chapters, and there is a good index. The type and printing are good, and the color plates excellent. The printing was done in Great Britain. The monograph should be in all medical libraries.

Oral Anatomy. By Harry Sicher, M D, professor of anatomy and histology, Loyola University School of Dentistry, Chicago College of Dental Surgery. 4°, cloth, 529 pp with 310 illustrations. St. Louis: C V Mosby Company, 1949. \$15.00.

The textbook is written primarily for dental students but should prove valuable to surgeons interested in the head and neck. It is not intended to supplant textbooks on human or dental anatomy, but to supplement them. The text is divided into two parts—descriptive and regional and applied anatomy—and deals with the head and neck. In the second part, among other topics, the anatomy of local anesthesia, arterial hemorrhages and ligation of arteries, the propagation of dental infections, tracheotomy and laryngotomy and the temporomandibular articulation are discussed. There is an extensive, comprehensive index. The type, printing and illustrations are excellent. The book is recommended for all medical libraries and should prove valuable to surgeons.

An Elementary Atlas of Cardiology. An introduction to electrocardiography and x-ray examination of the heart. By H Wallace-Jones, M D, M Sc, F R C P, honorary consulting physician, Royal Liverpool United Hospital. E Noble Chamberlain, M D, M Sc, F R C P, honorary physician, Royal Liverpool United Hospital and E L Rubin, M D, F F R, D M R E, honorary radiologist, Royal Liverpool United Hospital. 8°, cloth, 108 pp with 99 illustrations. Bristol, England: John Wright and Sons, Ltd., 1948. Incorporating the third edition of *Electrocardiograms*.

This elementary atlas was first published in 1939 as an *Atlas of Electrocardiography*. In this edition it has been enlarged to include a section on cardiac radiology. Some revision of the original text has been made including the addition of records showing Lead CR₁ in normal and abnormal rhythms. The section on auricular fibrillation has been rewritten in the light of the knowledge gained from this lead. The text is divided into two parts: electrocardiography com-

prising fifty pages, and radiography of the heart and large vessels, with forty-eight pages. The small atlas has been written primarily for medical students. The type printing and illustrations are excellent. The lack of an index is regretted.

Nursing Care of Neurosurgical Patients. By Roland M Klemme, M D, professor of surgery, Saint Louis University School of Medicine. 8°, cloth 117 pp with 61 illustrations. Springfield, Illinois: Charles C Thomas, 1949. \$3.00.

This manual for nurses incorporates the lectures of the author and is based on years of experience in the care of neurosurgical patients. There are chapters on anatomy of the brain and spinal cord and on clinical signs and symptoms, neuralgia, traumatic head injuries, the spine and spinal cord and miscellaneous neurosurgical procedures. The chapters on the scrub nurses table, materials and supplies and on instruments for operative procedures, give in detail the layouts for the different operations. An appendix provides special information of a general character. There is a good index. The volume is a fine example of good book making and should be included in all collections on neurology and should be in all medical libraries.

Aviation Medicine in Its Preventive Aspects. An historical survey. By John F Fulton, O B E, M D, D Sc, Sterling professor of physiology, Yale University. 8°, cloth, 174 pp, with 43 illustrations. New York: Oxford University Press, 1948. \$3.50.

Dr Fulton, in 1947, delivered the Heath Clark lectures at the London School of Hygiene and Tropical Medicine. These lectures are now printed in this small volume and constitute a valuable contribution to aviation medicine. The five lectures considered altitude sickness and acclimatization (the history of oxygen), decompression sickness (the genesis of the tissue bubble), pressure cabins and explosive decompression (the spring of the air), effects of acceleration (dim-out and black-out protective measures) and man and the machine (problems of safety in flight). In these various lectures Dr Fulton has outlined the history of the topics from the time of Robert Boyle to the present. Each chapter is well documented with a long list of pertinent references. The publishing is of the highest type. The book should be in all public and medical libraries.

Symptoms in Diagnosis. By Jonathan C Meakins, C B E, M D, D Sc, LL D, F R S (Edinburgh), F R S (Canada), F R C P (London), F R C P (Edinburgh), Hon F R C S (Edinburgh) and F R C P (Canada). Second edition. 8°, cloth, 542 pp. Baltimore: Williams and Wilkins Company, 1948. \$7.50.

This standard monograph, first published in 1941, has been rewritten for this second edition. More than a third of the chapters were written by colleagues of the author. The material is arranged according to the organs and systems of the body and concludes with a chapter on psychiatry. There is a good index and the publishing is excellent. The book should be available to all clinicians and should be in all medical libraries.

An Atlas of Bone-Marrow Pathology. By M C G Isaacs, M Sc, M D, M R C P, lecturer and deputy director, Department of Haematology, The University and Royal Infirmary, Manchester. 8°, cloth, 79 pp, with 3 illustrations and 12 plates. Illustrations by D Davison, medical artist to the University of Manchester. New York: Grune and Stratton, 1948. \$6.50.

This special atlas consists of fifty-two pages of text and twelve excellent color plates. It seeks to provide an accurately illustrated account of the bone marrow in health and disease. The material is well arranged and deals with the nomenclature and development of the blood cells, the technic of sternal puncture, the morphology of the marrow cells, the normal bone-marrow puncture, bone-marrow changes in disease, the bone-marrow in infants and children and differential diagnosis and indications for sternal puncture. There is a bibliography of seventy-seven titles and also a combined index to the text and plates. The printing of text and plates was done in Great Britain.

The Hospital in Contemporary Life Edited by Nathaniel W. Faxon, M.D., director, Massachusetts General Hospital 8°, cloth, 288 pp. Cambridge Harvard University Press, 1949 \$5.00

This symposium by eight Boston authorities comprises the following topics: the development of the hospital, the relief of suffering, human nature and the understanding of disease, the care of the patient, the education of the doctor, how medicine grows and its relation to science, unsolved problems and the place of the hospital in the social order. There is a good index. The book is well published and should be in all medical and social libraries.

Social Medicine: Its derivations and objectives The New York Academy of Medicine Institute on Social Medicine, 1947. Edited by Iago Galdston, M.D. 8°, cloth, 294 pp. New York Commonwealth Fund, 1949 \$2.75

This small volume contains the papers read by twenty-six persons at the Institute. The material is divided into seven parts: changing concepts of the relation of medicine to society, the history of social medicine, social medicine—its differentiation from and relation to clinical and preventive medicine, epidemiology in social medicine, the place of nutrition in social medicine, social psychiatry and social medicine, social applications of psychiatry, and social medicine—the appeal to the common man by Lord Horder. The publishing is excellent. The lack of an index in a Commonwealth Fund publication is surprising. The book should be in all medical and social libraries.

The Physiology of the Eye By Hugh Davson, D.Sc. (London). With a foreword by Sir Stewart Duke-Elder, K.C.V.O., M.A., D.Sc., Ph.D., M.D., F.R.C.S. 8°, cloth, 451 pp., with 301 illustrations. Philadelphia: Blakiston Company, 1949 \$7.50

This textbook provides in a compact form the information on the physiology of the eye and on optics needed by the student and optician. The text was printed in Great Britain and bound in the United States. The material is well arranged, and the printing well done with a good type. The volume should prove useful to the persons for whom it was written.

Flight from Reality By Norman Taylor 8°, cloth, 237 pp. New York: Duell, Sloan and Pearce, 1949 \$3.50

This popular book relates the story of the misuse of the narcotics, as well as of alcohol, coffee, chocolate and tea.

NOTICES

ANNOUNCEMENTS

Dr. G. Marshall Crawford announces the association of Dr. Robert F. Tilley in the practice of dermatology and syphilology at 1180 Beacon Street, Brookline.

Dr. Frank M. Heifetz announces the opening of his office for the practice of otolaryngology at 174 Central Street, Lowell.

Dr. Edward J. Twigg announces his association with Dr. Philip S. Marcus for the practice of anesthesiology and diagnostic and therapeutic nerve blocks at 270 Commonwealth Avenue, Boston.

WOMAN'S AUXILIARY TO SUFFOLK DISTRICT MEDICAL SOCIETY

The November meeting of the Woman's Auxiliary to the Suffolk District Medical Society will be held in Sprague Hall, Boston Medical Library, on Thursday, November 3, at 2:30 p.m. The speaker for the afternoon will be Dr. Arthur W. Allen, president of the Massachusetts Medical Society. Tea will be served after the meeting.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held in the classroom of the Nurses' Residence on Thursday, November 3, at 7:15 p.m. Dr. Langdon Parsons will speak on the subject "Present-Day Concept of Carcinoma of the Cervix." Dr. Rosemary Nelson will be chairman.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be held at the Massachusetts General Hospital, Boston, on Monday, November 7, at 8:15 p.m., Dr. Edward F. Bland presiding.

PROGRAM

The Blood and Interstitial Fluid Volumes after Sympathectomy for Hypertension. Dr. Fiorindo A. Simone.

A Study of the Castrate Male: Its contribution to cardiovascular research. Dr. Menard M. Gertler and Stanley M. Garn, Ph.D.

The Clinical Response of Rheumatic Fever and Acute Carditis to ACTH. Drs. Benedict F. Massell, Joseph E. Warren, George P. Sturgis, Buford Hall and Ernest Craige.

Further Experience with a Venous Shunt for Advanced Mitral Stenosis. Drs. Edward F. Bland and Richard H. Sweet.

Electronic Mapping of the Heart. Drs. Conger Williams and Fred Alexander and Stanford Goldman, Ph.D.

The National Heart Program: A progress report. Dr. Paul D. White.

Interested physicians and medical students are cordially invited to attend.

NATIONAL TUBERCULOSIS ASSOCIATION

The forty-sixth annual meeting of the National Tuberculosis Association will be held April 24-28, 1950, at the Hotel Statler, Washington, D.C. The American Trudeau Society, the Medical Section of the Association, and the National Conference of Tuberculosis Secretaries, an organization of public-health workers, will meet concurrently with the Association.

The medical sessions will be devoted to four major fields: the chemotherapy of tuberculosis, surgical aspects of tuberculosis, laboratory investigations and nontuberculous diseases of the chest. Tentative plans for the public-health sessions include discussion of the nonhospitalized patient, evaluation of community-wide programs, elements in a community health program and new developments in community health organization.

Both scientific and public-health exhibits will be displayed throughout the meeting.

Further information may be obtained from the National Tuberculosis Association, 1790 Broadway, New York 19, New York.

EDWARD K. DUNHAM LECTURES

Christopher Howard Andrewes, F.R.S., head of the Department of Bacteriology and Virus Research at the National Institute for Medical Research, Hampstead, London, will deliver three lectures in the amphitheater of Building D, Harvard Medical School, at 5 p.m., on the general subject "Adventures among Viruses," under the Edward K. Dunham Lectureship for the Promotion of the Medical Sciences. The dates and subjects of the lectures are as follows:

Thursday, November 3 Some Properties of Viruses
Tuesday, November 8 Epidemic Influenza
Thursday, November 10 The Puzzle of the Common Cold

(Notices concluded on page xv)

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PULMONARY EMBOLISM*

A Statistical Study of Post-Mortem Material at the Massachusetts General Hospital

BENSON B. ROE, M.D.,† AND JOEL C. GOLDTHWAIT, M.D.‡

BOSTON

CONSIDERABLE interest has been manifested in the subject of thromboembolism during the past few years, and numerous reports have appeared in the literature on the various preventive measures. As far as we know, however, no long-range mortality statistics following an extended trial of one method of treatment have been reported, and it is our purpose here to analyze the possible effects of femoral-vein interruption on the mortality of pulmonary embolism at the Massachusetts General Hospital.

Interruption of the femoral veins was introduced in this hospital in 1939 as a measure hoped to be of value in the prevention of fatal pulmonary embolism. The procedure was employed in selected cases during the four-year period from 1939 to 1942, and the results¹ from this small group were sufficiently encouraging that a large-scale program was undertaken in the attempt to obliterate or to reduce the mortality from this distressing complication. Special attention was given to the problem, and more careful vigilance for the manifestations of pulmonary infarction and thrombophlebitis in the deep leg veins was maintained on both general surgical services and later to a large extent throughout the hospital. Bilateral interruptions of the femoral veins were done in large numbers for minimal indications and later (see Table 1) on an even greater scale with the addition of prophylactic interruptions in older age groups. Earlier reports²⁻⁶ have attempted evaluation of this immense effort from a clinical standpoint. It is the purpose of this paper merely to report the autopsy statistics for the five-year period 1943 through 1947, during which 1929 bilateral femoral-vein interruptions were done, as compared with similar earlier periods before the advent of specific preventive measures. Our two control series are taken prior to 1941, and

the period between 1941 and 1943 is omitted because vein interruptions were done on such a small scale as to have no significant effect on the whole hospital mortality rate.

The material for this study was obtained from the autopsy protocols from 1930 through 1947 and from the hospital records of patients. No case that did not come to autopsy was used, and every case with the autopsy finding of pulmonary embolism was reviewed. Classification of the data was difficult and necessarily arbitrary, but similar criteria were used in the comparative series. We were impressed with the large personal element in evaluat-

TABLE 1 *Incidence of Therapeutic and Prophylactic Femoral-Vein Interruption in 1929 Cases at the Massachusetts General Hospital*⁶

YEAR	THERAPEUTIC OPERATIONS	PROPHYLACTIC OPERATIONS	TOTALS
1943	150	15	165
1944	208	72	280
1945	214	178	392
1946	259	289	548
1947	227	317	544
Totals	1058	871	1929

ing the records and protocols, as well as the variability of details within them, and, therefore, must urge caution in the use of these figures in comparison with other series.

To eliminate the cases of doubtful significance and the question of incomplete autopsy dissection, we have listed separately all cases in which the embolus or emboli were small and improbable as the cause of death. The remaining cases of fatal embolism were further divided into two groups: the first with massive emboli unquestionably lethal, and the second with large emboli considered to be of fatal magnitude (labeled "Large ? Fatal") but open to some challenge as the actual cause of death because of an atypical terminal clinical course or the presence of other fatal disease of equal or greater magnitude.

*From the Department of Pathology and Bacteriology, Massachusetts General Hospital.

†Assistant resident surgeon, Massachusetts General Hospital.

‡Assistant resident in medicine, Veterans Administration Hospital, West Roxbury, formerly assistant resident in pathology, Massachusetts General Hospital.

The findings of the three five-year periods — 1931 through 1935, 1936 through 1940 and 1943 through 1947 — are tabulated below. The total number of autopsies in each period was about the same, and it seems reasonable to assume that these are equally representative major samples of total deaths. The sharp increment of small emboli from 2.2 per cent in the first period to 5.4 per cent in the second, as pointed out in the third column of Table 2, is undoubtedly attributable to the focus of attention in the pathology laboratory on this problem and consequent emphasis on more complete routine

emboli, and hence the totals, showed a steady and appreciable increase, which was exactly the same (2.7 to 3.5 per cent) in the recent period as that between the first and second control periods (1.9 to 2.7 per cent), as shown in the fourth column of Table 2.

The steady increase of deaths from pulmonary embolism in spite of venous interruptions can perhaps be explained on the basis of the relative decline of other diseases and complications with the advent of chemotherapy, blood banks, improved technics and so forth, as well as the rising number

TABLE 2 *Incidence of Pulmonary Embolism in Total Autopsies (Massachusetts General Hospital)*

DATE	NO OF AUTOPSIES	CASES WITH SMALL, INCIDENTAL EMBOLI		CASES WITH FATAL EMBOLI					
		no	percentage	no	percentage	no	percentage	no	percentage
1931 1935	1,991	43	2.16	37	1.86	15	0.75	52	2.16
1936 1940	1,832	99	5.40	49	2.67	18	0.98	67	3.66
1943 1947	2,083	111	5.33	73	3.50	19	0.91	92	4.42

dissection of the pulmonary vascular tree. It is our impression, however, that these figures are still unreliable because of the variability of this routine and the difficulty of standardizing the pathologist's interpretation. For this reason we have included under "small" all emboli described as lodging in secondary or smaller branches of the pulmonary artery even though some of them were

of older patients in the hospital census. In addition, it has been suggested that the increasing number of cancer patients and the greater magnitude of surgery are responsible for this increase although it is notable that thromboembolism appears through a wide range of age, primary disease, and operative procedure (see Tables 5, 6 and 7). Statistical evaluation of these changing factors is impractical if

TABLE 3 *Analysis of Deaths from Pulmonary Embolism*

PERIOD	TOTAL ADMISSIONS	TOTAL AUTOPSIES	TOTAL DEATHS FROM PULMONARY EMBOLISM		CASES OF ADVANCED INCURABLE CANCER		DEATHS THAT SHOULD HAVE BEEN PREVENTED	
			MASSIVE FATAL EMBOLISM	LARGE ?FATAL EMBOLISM	MASSIVE FATAL EMBOLISM	LARGE ?FATAL EMBOLISM	MASSIVE FATAL EMBOLISM	LARGE ?FATAL EMBOLISM
1931-1935	67,038	1,991	37	15	3	2	34	13
1936-1940	78,065	1,832	49	18	5	1	44	17
1943-1947	79,951	2,083	73	19	13	4	60	15

extensive enough to suggest at least a precipitating cause of death. The ones considered to be probably or definitely fatal were described as organized clots lying in and occluding no less than two primary branches of the right or left pulmonary artery so as to block a major portion of the pulmonary circulation. Subdivision of the large emboli as described above was more or less arbitrary but where there was any reasonable doubt they were listed under "Large ? Fatal." It is interesting that these disputable cases remained very constant between the three periods and probably are a source of less inaccuracy than we feared. The massive

not impossible, and we can but recognize their influence on the net result.

Further to analyze the comparative statistics between the preligation era and the recent series, we were obliged to introduce corrective factors as much as possible. It must be taken into account that during the recent period of venous interruptions the procedure was considered but not done in many cases in which advanced incurable malignant lesions seemed to contraindicate strenuous preventive measures. We therefore separated these cases from both series (see Table 3) to arrive at a figure of deaths from pulmonary embolism that

it would be desirable to prevent. This figure in the last series, however, can further be challenged as not representing the failures of the whole program of venous interruption since the doctrines of such a program could hardly receive universal acceptance in an institution of this size. It is pointed out that deaths from pulmonary embolism occurred in patients on private services and specialty services who had indications for venous interruption under the precepts of the more vigorous policy. It was therefore necessary to review all the clinical records in the cases of fatal embolism and separate from the previous figure the cases in which, in retrospect, there had been signs suggestive of warning pulmonary infarction or venous thrombosis in the legs according to the criteria used by the peripheral vascular service*. We were also obliged to rule out the autopsies on patients whose embolic episode occurred outside the hospital, where early diagnosis may have been overlooked and prompt venous interruption was impossible. The remaining number of deaths from pulmonary embolism after the "corrections" represents the failures of the over-all program, assuming it to have been properly executed throughout the hospital.

It is evident, then, that all the autopsy percentages fall within the same range, and the lower figure of 2.54 per cent for the recent period is not significantly smaller than the preceding one.

It must be pointed out that these figures demonstrate not only the effect of so-called "therapeutic" venous interruption on thromboembolic mortality but also the sum total effect of all preventive

singly. Not only has the total figure for this period been unchanged but figures for individual years† have remained surprisingly constant despite the recent — during the past two years — increased use of prophylactic interruptions and anticoagulants‡.

It has not been our purpose to evaluate so-called "prophylactic" venous interruption but as a corollary to Table 3 it is interesting to point out that of the 53 total net deaths in the last period 14 fell into the category that, in retrospect, would have received prophylactic interruption according to the proponents of this more recent measure§. Application of this figure to the above data has not been made and would hardly be judicious except in the most theoretical sense because of the narrower scope of the procedure, but if one accepted this added correction, as well as the assumption that venous interruption would prevent all emboli the net total deaths would be reduced from 53 to 39, which would drop the incidence to a significantly lower figure 1.87 per cent.

FATAL PULMONARY EMBOLI FOLLOWING FEMORAL-VEIN INTERRUPTION

In the course of this study a group of patients was collected in the recent five-year period who had received bilateral femoral-vein interruption, either superficial or common, and who also had an anatomic diagnosis of pulmonary embolism at autopsy. This group was included in the above series, but we believe that further analysis of these cases is warranted. The group included a total of

TABLE 3 (Continued)

CASES WITHOUT VENOUS INTERRUPTION BUT WITH INDICATIONS IN RETROSPECT		CASES WITH ONSET OF SIGNS OUTSIDE HOSPITAL		NET DEATHS			PERCENTAGE OF AUTOPSIES	PERCENTAGE OF ADMISSIONS
MASSIVE FATAL EMBOLISM	LARGE FATAL EMBOLISM	MASSIVE FATAL EMBOLISM	LARGE FATAL EMBOLISM	MASSIVE FATAL EMBOLISM	LARGE FATAL EMBOLISM	TOTALS		
—	—	—	—	34	13	47	2.36 ($\pm 0.34^*$)	0.07
—	—	—	—	44	17	61	3.33 ($\pm 0.42^*$)	0.08
11	2	7	2	42	11	53	2.54 ($\pm 0.34^*$)	0.07

*Calculated standard error of percentage

measures exercised. Early ambulation, prophylactic interruptions and anticoagulants unquestionably play an important role, but they obviously cannot be separately evaluated from this material. However, since there had been no significant change in the mortality figures in the presence of all factors, it seems reasonable to assume that there would have been no significant change had these factors acted

26 cases. Of these 16 were discarded for the following reasons: in 1 case the emboli were composed of tumor from a renal-cell carcinoma, in 6 cases the emboli were considered small enough to be incidental as a cause of death, in 5 cases the embolus might have been the immediate cause of death, but was not classified as such because of its size

*Bilateral interruptions of the superficial femoral veins were done as an emergency procedure on any patient with otherwise unexplained signs of deep-calf or popliteal tenderness, measurable calf or ankle swelling, localized pulmonary consolidation by x-ray study unless interpretation could rule out infarct, sudden chest pain or hemoptysis or both (even with negative x-ray examination) and in many cases when simultaneous rise of temperature, pulse and respiration was accompanied by minimal or equivocal evidence of one or more of the above.

†Total deaths from thromboembolism by years were 1943 15 1944 25 1945 12 1946 15 and 1947 2.

‡In all over 800 patients received Dicumarol in some dosage through 1947.

§Prophylactic bilateral interruptions of the superficial femoral veins were done on patients over sixty years of age preceding or within forty-eight hours of a major surgical procedure and in certain younger patients such as those with peritonitis who were to be immobilized in Fowler's position.

or the importance of other diseases (uremia, peritonitis and so forth), and in 4 cases the clinical course suggested that massive embolism had occurred

significance, that the group contained no cases of congestive heart failure. The fatal embolism in Case 3, which followed an eye operation, suggested

TABLE 4 Data in Clear-Cut Cases of Massive Fatal Embolism following Femoral-Vein Interruption

PATIENT	AGE	PRIMARY DISEASE	REASON FOR INTERRUPTION	CLOTS FOUND AT OPERATION	INTERVAL FROM INTERRUPTION TO DEATH	SOURCE OF FATAL EMBOLUS
M McD	75	Thrombophlebitis deep veins of legs	Leg signs	Yes	11 days	Unknown (restricted autopsy)
C S	74	Carcinoma of colon with metastases	Pulmonary infarct 3 days after pentoneoscopy	No	8 days	Left deep femoral vein occluded at junction of middle and lower thirds
C B	70	Cataracts	Pulmonary infarct 3 days after eye operation	No	2 days	Thrombi in left common femoral, internal and common iliac and right common iliac veins
L B	62	Incisional hernia in scar of hysterectomy obesity	Prophylactic interruption 2 days after hernia repair	No	13 days	'Currant jelly clot' in 3-cm. stump of superficial femoral on left attached to this 8 cm. of red gray laminated thrombus in common femoral vein otherwise clear
E M	74	Diabetes mellitus gangrene of toes	Prophylactic interruption 2 days after low thigh amputation*	No	2 days	Thrombus in 1-cm. stump of right superficial femoral vein continuous with 7-cm. clot in common femoral vein otherwise clear
W D	42	Subarachnoid hemorrhage	Interruption on 2nd hospital day because of calf tenderness	Yes (right side only)	13 days	Right common femoral vein ligated this and iliac vessels thrombosed to mouth of vena cava left side clear
J P	78	Arteriosclerotic gangrene of foot	Prophylactic interruption at time of low thigh amputation	No	2 hr	No thrombus found in common femoral veins or deep femoral veins 8 cm. below sites of operation
G C	68	Carcinoma of colon	Prophylactic interruption on 5th hospital day 5 days after oostomy	No	17 days (8 days after resection)	Iliac common and deep femoral veins clear as far as examined—8 cm. below operative sites
F B	77	Thrombophlebitis with pulmonary infarct 1 day prior to admission	Pulmonary infarct interruption on day of admission	No	13 days	Thrombosis of left external iliac common and deep femoral veins thrombus 0.5 cm in diameter at ligation site on right.
D S	54	Carcinoma of stomach	Prophylactic interruption 2 days after total gastrectomy	No	32 days	Thrombi 2 cm. long extending into common femoral vein from each interruption site

*Because at autopsy the clot in the common femoral vein was considered to be several days old and thus probably antedating interruption the procedure was classified as 'inadequate therapy' in retrospect

prior to the venous interruption. The remaining 10 cases in which there was a clear-cut picture of massive fatal pulmonary embolism following venous interruption are discussed in Table 4.

It is apparent that there is nothing remarkable about the age and sex distribution in these cases, all but 2 patients were over sixty years of age. The

that the operative procedure itself was probably of little significance.

Five patients in this group had venous interruptions for prophylactic reasons, but one of these cases was later reclassified under therapeutic (see footnote in Table 4), 3 were done after a warning pulmonary infarct, and 2 because of thrombophle-

TABLE 5 Incidence of Fatal Pulmonary Emboli by Age Groups

AGE	1931-1935			1936-1940			1943-1947		
	MASSIVE FATAL EMBOLI	LARGE ?FATAL EMBOLI	TOTALS	MASSIVE FATAL EMBOLI	LARGE ?FATAL EMBOLI	TOTALS	MASSIVE FATAL EMBOLI	LARGE ?FATAL EMBOLI	TOTALS
57									
0-19	0	1	1	0	0	0	0	0	0
20-29	0	2	2	1	1	2	1	1	2
30-39	2	1	3	4	0	4	2	1	3
40-49	6	1	7	5	1	6	8	4	12
50-59	9	1	10	12	4	16	16	3	19
60-69	8	6	14	9	9	18	22	3	25
70-79	10	2	12	16	3	19	18	6	24
80-89	2	1	3	2	0	2	5	1	6
90-99	0	0	0	0	0	0	1	0	1
Totals	37	15	52	49	18	67	73	19	92

primary disease seemed to represent a fair random sample of that found in the whole group of fatal pulmonary emboli. It is of interest, but of doubtful

bitis in the deep venous system of the legs. Clots were found in the veins at operation only in the last 2 cases. In the 4 cases classified as prophylactic

interruptions, 1 patient was found at autopsy to have a blind stump of the superficial femoral vein in which a clot had developed and propagated into the common femoral vein. One patient had both superficial femoral veins tied flush with no pouches

FATAL PULMONARY EMBOLISM WITHOUT WARNING

It is of interest that a breakdown of the 92 deaths from pulmonary embolism in the recent five-year period reveals that 49 or 53 per cent occurred with-

TABLE 6 *Distribution of Fatal Pulmonary Emboli according to Primary Disease*

PRIMARY DISEASE	1931-1935		1936-1940		1943-1947	
	MASSIVE FATAL EMBOLI	LARGE FATAL EMBOLI	MASSIVE FATAL EMBOLI	LARGE FATAL EMBOLI	MASSIVE FATAL EMBOLI	LARGE FATAL EMBOLI
Gastrointestinal tract and biliary system						
Benign	12	1	3	0	4	2
Malignant	4	1	5	2	14	1
Malignant with metastases	1	0	4	1	10	1
Gynecologic system						
Benign	2	0	4	0	4	0
Malignant	0	0	0	0	3	0
Malignant with metastases	1	2	1	0	0	1
Genitourinary system						
Benign	9	1	4	2	2	0
Malignant	3	1	6	1	1	0
Malignant with metastases	0	0	0	0	1	1
Chest						
Benign	1	0	0	0	5	2
Malignant	0	0	0	0	3	0
Hernias	0	0	2	0	2	0
Breast lesions	1	1	0	1	2	0
Cardiovascular disease	1	5	4	6	6	6
Peripheral vascular disease	1	0	1	1	3	2
Thrombophlebitis	0	0	3	0	1	1
Miscellaneous (neurosurgical, orthopedic and eye conditions and so forth)	1	3	12	4	12	2
Totals	37	15	49	18	73	19

and yet thrombi were found adherent to the ligation site on both sides. The other 2 patients had no clots demonstrated in the leg veins.

These 10 patients represent a mortality rate of 0.5 per cent in the over-all program of 1929 bi-

out any clinical warning whatsoever (that is, no signs of pulmonary infarct or thrombophlebitis). In some cases, of course, the record makes no specific reference to signs that may have gone unnoticed (it should be pointed out again, however,

TABLE 7 *Distribution of Fatal Pulmonary Emboli according to Operation*

OPERATION	1931-1935		1936-1940		1943-1947	
	MASSIVE FATAL EMBOLI	LARGE FATAL EMBOLI	MASSIVE FATAL EMBOLI	LARGE FATAL EMBOLI	MASSIVE FATAL EMBOLI	LARGE FATAL EMBOLI
Exploratory laparotomy	4	2	4	0	5	0
Resection or exteriorization of gastrointestinal tract	6	1	7	2	20	1
Appendectomy or drainage of appendiceal abscess	1	1	0	0	2	0
Cholecystectomy	5	0	2	0	2	0
Herniorrhaphy	0	0	2	0	2	0
Procedures on uterine and ovaries	1	0	4	0	4	0
Procedures on kidneys, adrenal glands and ureters	2	0	5	0	1	0
Procedures on bladder and prostate	9	1	5	2	3	0
Exploratory thoracotomy	0	0	0	0	3	0
Empyema drainage	1	0	0	0	0	0
Trans thoracic procedure	0	0	0	0	(3*)	0
Amputation	1	0	1	0	2	0
Mastectomy	1	1	0	1	1	0
Miscellaneous (neurosurgical, orthopedic and eye procedures and so forth)	1	0	5	0	10	3
Pentoneoscopy	0	0	0	0	1	0
Totals	32	6	36	5	64	4

*These were all operations on the esophagus or stomach and are included under the heading "Resection or Exteriorization of Gastrointestinal Tract."

lateral femoral-vein interruptions. The 4 prophylactic interruptions in this group represent a 0.5 per cent mortality among the 871 prophylactic interruptions done during that period.

that the entire house staff was aware of the problem during this period, and most of the records contained periodic notes about leg and chest examinations. Of the remaining 43 patients 25, or

27 per cent, were known to have had one or more warnings, either in the legs or by pulmonary infarct, but the records on the ante-mortem course of the other 18 cases are incomplete or absent

the Lahey Clinic, reported premonitory signs in 85 per cent of their fatal cases. One can only speculate over this discrepancy. Perhaps its cause is the successful surgical treatment of patients with warning infarcts or thrombophlebitis. However, there is apparently considerable variation in the criteria used for "warning," and this should be considered seriously as the principal cause. We did not believe that a review of the hospital records in the period before venous interruption would provide a suitable comparison because so little attention was focused on the problem that the signs were probably more often missed than recorded.

DISTRIBUTION OF FATAL EMBOLISM

Table 5, 6 and 7 are presented as supplementary information gathered during the course of this study and do not have any direct bearing on the more pertinent over-all figures. However, the distribution of fatal pulmonary embolism is of considerable interest, and although our figures in each group are too small for individual analysis the material may prove useful in the compilation of more extensive data.

Age

That pulmonary embolism is a disease more common in the older age groups is demonstrated in Table 5. It is significant, however, that approximately 20 per cent of all fatal emboli occurred in ages below fifty, in which total deaths were less numerous. Thus, if the ratio of deaths from pulmonary embolism is plotted in relation to total deaths, or autopsies (Fig 1), there is a more slowly rising curve, which supports the initial statement but which also emphasizes the wide age distribution of the disease.

It is interesting that comparison between these curves for the different periods studied shows no dramatic shift that could be interpreted as an effect of preventive measures. In fact, if anything, there is a shift toward the higher age groups in the recent period despite concentration of preventive efforts on this group. This is probably due to the constant increase in the average age of patients admitted (a sample study from 1930 and 1943 [thirteen years] showed an increase of eight years).

Primary Disease

The deaths from pulmonary embolism have been further analyzed in Table 6 and 7 with regard to the primary disease and operative procedure with which they were associated.

It should be made clear that comparison between any two figures in these tables cannot be considered valid since there is no statistically significant difference between them according to sample statistical analysis. However, Table 6 shows that massive fatal pulmonary embolism occurs in a

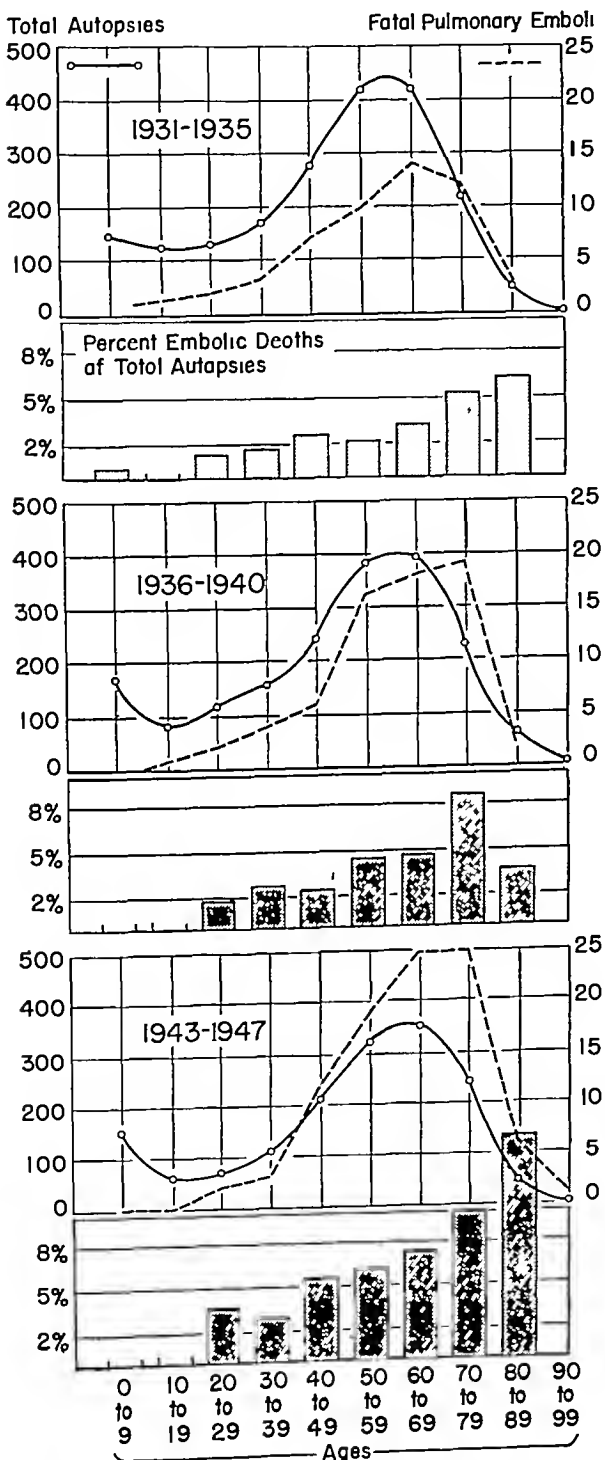


FIGURE 1 Distribution of Autopsies and Pulmonary Emboli by Age Groups

This figure of unheralded fatal emboli is somewhat higher than that given in other reports. DeTakats⁷ states that one fifth to one fourth of emboli are fatal at first occurrence, and Evans and Dee,⁸ of

wide variety of diseases and that although a few are found in medical conditions, the majority of emboli complicate surgical disease and occur during the postoperative period. Comparison of the totals in Table 6 and 7 demonstrates this fact.

The decline of pulmonary embolism as a complication of benign conditions of the gastrointestinal and biliary tracts is more apparent than real, being exaggerated by a combination of many different types of disease under one heading. The same reservation can be made for benign conditions of the genitourinary system, although in both these categories it is undoubtedly true that operative procedures are not so formidable and convalescence not so prolonged as they were fifteen years ago. The increasing number of patients with pulmonary embolism complicating malignant lesions of the gastrointestinal and biliary systems is probably a reflection of the increased number of patients with cancer in the hospital population. We have not analyzed this in more detail because, considering the questionable significance of the figures as they stand, nothing would be contributed by such a study.

Also of interest is the fact that diseases in which the treatment has been fairly standardized for many years (uterine fibroids, hernias and lesions of the breast) show an apparently constant incidence of embolism.

It should be noted that the absence of fracture cases in this list is due to the fact that all such deaths came under the jurisdiction of the medical examiner and do not appear in our autopsy files.

Operative Procedure

In similar fashion it is seen that fatal pulmonary emboli follow a wide variety of operative procedures. The chief point to be made in Table 7 is the fairly constant number of deaths from pulmonary emboli with the different procedures throughout the three periods. The increased number of fatal emboli following gastrointestinal-tract resection is probably accounted for by the increased number of patients in the hospital population subjected to operation for gastrointestinal cancer. The decrease following operations on the bladder and prostate has been attributed to femoral-vein interruption.*

In Table 5, 6 and 7 the obvious question arises over what these figures represent in terms of ratio to total hospital population by age group, total patients treated in each disease category and total operations performed in each category. These data, however, were not readily available and are essentially beyond the scope of this paper, which is an analysis of autopsy figures only.

Discussion

In an evaluation of this study it becomes evident that the incidence of pulmonary embolism is affected by a complex interplay of factors. The introduction of femoral-vein interruption is only one of many

considerations, and the impossibility of evaluating separately the other factors makes it equally impossible to evaluate the effect of one method in terms of the sum total.

It can be said, however, that a five-year, large-scale program of femoral-vein interruption has failed to alter significantly the mortality figures for pulmonary embolism as compared with earlier, similar periods.

The problem is further confused by the introduction of conflicting factors, which have tended to increase the incidence of thromboembolism during the same period of preventive efforts. Some of these are technical and therapeutic advances that have reduced other fatal complications and kept sick patients alive for a longer period in which to develop venous thrombi, an increasing number of geriatric patients, in whom pulmonary embolism is more common, an increasing proportion of cancer patients in this hospital, also with a somewhat higher incidence, and more heroic surgical procedures from which convalescence is often prolonged and complicated. The extent to which these factors have actually promoted thromboembolic disease cannot be accurately determined*, however, if their effect has been appreciable it might be postulated that a higher expected mortality rate has been kept down by the preventive program. It is regrettable that our controls had to be taken from a virtually different era rather than a comparable set of circumstances, but no group sufficiently large for comparison was deprived of some preventive measure.

Mortality statistics alone are not a satisfactory criterion for evaluating a procedure, and it should be pointed out that clinical analysis of selected patients demonstrates more favorable results from femoral-vein interruption in preventing fatal pulmonary embolism. The continued high incidence of the disease at the autopsy table, however, suggests that the problem remains unsolved.

SUMMARY

At the completion of a five-year program of femoral-vein interruption, autopsy statistics of pulmonary embolism are reviewed for this period and compared with those for two previous five-year periods.

These figures are analyzed and corrected in an attempt to demonstrate more accurately the effect of the program.

Analysis is made of the pulmonary embolic deaths that followed femoral-vein interruption.

Data are presented on the distribution of fatal emboli by age group, primary disease and operative procedure.

*To demonstrate the magnitude of these changes a sample analysis was made from reports of the general surgical service for the contrasting two year periods: 1930-31 and 1946-47. In brief it was found that the average age at death has risen from 49.3 to 57.6 years; surgical admissions for malignant lesions have risen from 28 to 44 per cent, whereas admissions for inflammatory disease have decreased relatively from 28 to 14 per cent and sepsis as a fatal complication on surgical patients has declined from 63 to 37 per cent (of all deaths).

No significant improvement in the mortality figures for pulmonary embolism in the hospital as a whole could be demonstrated in the period of venous interruption

Because of the many considerations that defied statistical analysis and the inadequacy of control data, no conclusions can be drawn either to support or to negate the value of the program

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PLASTIC OPERATION ON THE FALLOPIAN TUBE

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DURING the past fifteen years there has been an increasing interest in the problem of sterility. One of the more difficult obstacles in this field has been occlusion of the oviducts. Rubin's¹ establishment of a diagnostic method for determining tubal patency enabled gynecologists to make a diagnosis of occlusion while hysterosalpingography accurately localized the point of obstruction. From 1932 to 1936 Solomons,² Bonney³ and Holden and Sovak⁴ presented encouraging reports concerning operative relief of sterility due to occluded tubes. As Solomons put it, "an occasional good golf shot impels the worst player to persist with the game, so occasional successes impel me and others to try further." However, enthusiasm for the tubal plastics lessened since results were poor, and some authors even discouraged further attempts.

Recently those interested in the problem have stated that even though only 5 to 10 per cent of these women become pregnant postoperatively, an operation is well worth while, after conservative therapy by repeated carbon dioxide insufflation, heat by diathermy or Elliot bag or estrogenic hormone stimulation has been tried. The discovery of nonpatent tubes during a sterility study on many of my own patients stimulated me to look up the results obtained by operative procedures. Twenty-three patients were operated upon at the Massachusetts General and Palmer Memorial hospitals during the years 1932-1947, either on the ward service or in the private practices of Dr Joe V Meigs or Dr Langdon Parsons or myself. Of these, 5 had uterotubal implantations for bilateral cornual obstruction, after which 3 had a normal pregnancy and delivery. Eighteen patients had salpingostomies for occlusion of the fimbriated ends of the

tubes, and in these cases no pregnancies have occurred.

The first tubal implantation was performed and recorded by Watkins⁵ in 1896, and the patient had a subsequent pregnancy and miscarriage. In 1921 Shaw⁷ described a successful tubal implantation performed by Cullen. Solomons² reported 6 pregnancies following this procedure. Holden and Sovak⁴ discussed 3 cases of tubal implantation with 1 subsequent normal pregnancy, and Sovak⁴ later reported another of their cases in which an ectopic pregnancy occurred with rupture of the tube. The accepted technic employed has been a division of the tubes at the point of occlusion, after which patency of the remainder of the tube is demonstrated by air and saline solution injection. The occluded cornual portion is reamed out with a special instrument or by sharp dissection. The patent tube is then pulled into the uterus and held there by stitches (Fig 1). Patency is again proved by air or water insufflation from the fimbriated end. The serious complications following this operation include exacerbation of pelvic inflammatory disease, and there is the possibility of uterine rupture during pregnancy at the site of implantation of the tube.

The first salpingostomy was reported by Martin⁶ in 1885. Nine years later Mackenrodt¹⁰ described the first 2 successful cases. The largest series in the literature is that of Solomons,² who in 1936 reported on 366 tubal operations—cornual, isthmic and fimbrial. Two tubal and 28 normal pregnancies occurred—that is, pregnancy was obtained in 8.2 per cent. Bonney reported 70 cases, with follow-up study in 37, in which 7, or 18 per cent, of patients conceived. The results of these operations have varied from 100 cases without a pregnancy¹¹ to 8 full-term pregnancies after 7 operations.¹²

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The technic of salpingostomy generally recommended is that of Holden and Sovak⁵—a modification of the circumcision operation devised by Bonney (Fig 2)⁴. The advantage of this operation is that bringing the mucosa back to the serosa for a distance of 1.5 to 2.5 cm closes the raw edge and the chances of adhesions and secondary closure are thereby lessened. The technic is as follows: the tube is handled without instruments and the fimbriated end is opened if possible by gentle, blunt dissection—or a small section of the dilated tube is resected. Patency is tested for with a glass syringe. A urethral catheter, No 5 Fr or a piece of polyethylene tubing, is threaded into the tube and a Bonney clamp applied to the tube 1.5 to 2.5 cm from the amputated end. A circular incision is made through the serosa and muscularis at the end of the Bonney clamp. Then, with two fine Allis clamps, the amputated end of the tube is gently pulled backward while the Bonney clamp is slowly

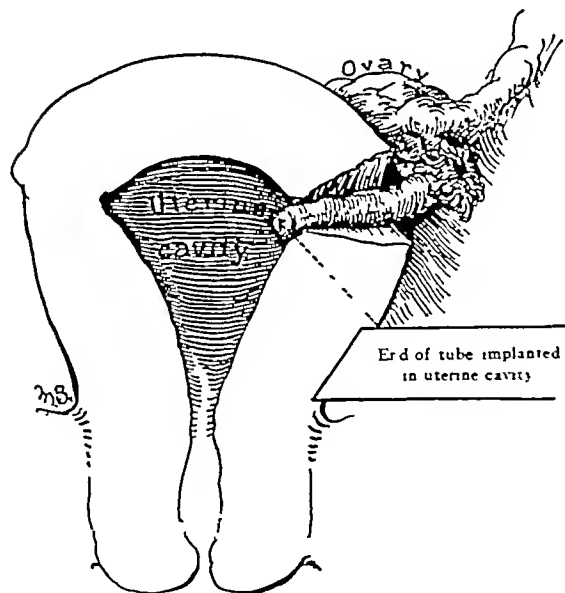


FIGURE 1 Implantation of the Outer End of the Fallopian Tube into the Uterine Cavity. (Reproduced from Shatz,¹ with the Permission of the Publisher.)

pushed forward. The tubal cuff so formed is held in place with fine catgut. Tubal patency is again established by the use of the syringe. The tube and ovary are then suspended by a stitch through the hilus of the ovary attached to the pelvic peritoneum. In the 18 salpingostomies reported here a simpler procedure of amputating the end of the hydrosalpinx and then suturing the mucosa to the serosa was employed. None of these patients became pregnant, although in 33 per cent of cases tubal patency was proved by the Rubin test or by hysterosalpingography postoperatively. The small diameter of the tube, the friable, infected

tissue and the tendency to bleed make it difficult to maintain an adequate lumen.

The serious complication after this operation has been an exacerbation of pelvic inflammatory disease. This occurred once in the 18 cases discussed here. If pregnancy results abortion sometimes occurs, and ectopic pregnancies have been reported. However, successful pregnancies do occur, and the risks are too slight to contraindicate the operation.

In the patients who had tubal operation three different pathologic conditions seemed to be con-

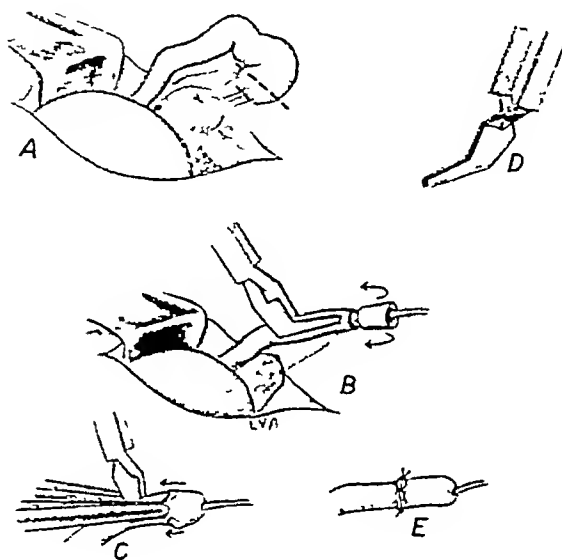


FIGURE 2 Technic of Salpingostomy. (Reproduced from Siegler,¹² with the Permission of the Publisher.)

cerned infection involving the endosalpinx, such as gonorrhea or tuberculosis, infections spreading through lymphatics and into the muscularis such as that after septic abortion, and infections around the tube—that is, perisalpingitis similar to that after a ruptured appendix.

In the 3 patients who became pregnant the infection was limited to the cornual segment of the tube. Success followed implantation because the diseased portion was easily resected. For example in Case 1 the infection started as endometritis occurring after abortion. At operation it was found that bilaterally only 2.5 cm of tube near the uterus was scarred and completely blocked. The remainder of the tube seemed to be of normal size, and the fimbriated ends were entirely free. In Case 3 the same cornual scarring was found. The left tube was otherwise normal. The right tube was also blocked at the fimbria. In the third successful case the block was limited to the cornua, as in Case 1.

In the other 2 cases with implantation into the uterus in which no pregnancy resulted, the cornua and the fimbriated ends of both tubes were involved, and according to the history the patients had had a much more severe post-partum infection. In the other 18 cases the fimbrial end of the tube was blocked by either gonorrheal infection or a pelvic peritonitis due to a ruptured appendix

the original infection the tube is abnormal and pregnancy impossible or, if pregnancy occurs, ectopic pregnancy is common.

The findings on the 23 patients operated upon are given in Table 1. In the 3 successful cases that resulted in living infants cornual resection and tubal implantation were performed. These cases are briefly presented below.

TABLE 1 *Results of Operation in 23 Cases*

CASE No	PATIENT	AGE	YEARS MARRIED	ETIOLOGY	PATHOLOGY	RESULT OF RUBIN TEST PREOPERATIVELY
1	V. K.	31	8	Sepsis after miscarriage	Bilateral cornual fibrosis	Tubes closed
2	R. U.	33	9	Salpingitis isthmica nodosa	Block at cornu, bilateral	Tubes closed
3	F. G.	30	2½	Peritonitis	Bilateral block at cornu, right fimbria closed	Tubes closed
4	C. A.	33	5	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges and cornual block	—
5	R. M.	24	1	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	—
6	J. W.	31	1½	Gonococcal pelvic inflammatory disease	Left tubo-ovarian abscess hydrosalpinx	Tubes closed
7	P. G.	29	4	Gonococcal pelvic inflammatory disease	Adhesions bilateral hydrosalpinges	—
8	B. E.	25	½	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	—
9	V. K.	28	5	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	Tubes closed
10	P. N.	31	5	Gonococcal pelvic inflammatory disease	Right tube gone left hydrosalpinx	Tubes closed
11	M. L.	23	2	Gonococcal pelvic inflammatory disease	Left hydrosalpinx	—
12	L. S.	19	5	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	—
13	E. P.	22	1½	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	—
14	E. M. O.	23	1	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges block at cornu	Tubes closed
15	E. T.	35	12	Gonococcal pelvic inflammatory disease	Right tube and ovary gone left hydrosalpinx second operation — left tube closed	Tubes closed
16	R. S.	19	— (single)	Gonococcal pelvic inflammatory disease	Right hydrosalpinx and cornual block left hydrosalpinx	—
17	M. D.	33	6	Post-partum infection	First operation, adhesions and bilateral hydrosalpinges second operation bilateral cornual block	Tubes closed
18	F. K.	34	8	Pelvic inflammatory disease after miscarriage	Bilateral hydrosalpinges 2.5 cm. from cornu on right	—
19	A. L.	20	2	Post partum pelvic inflammatory disease	Bilateral hydrosalpinges	—
20	L. T.	26	10	Pelvic inflammatory disease after miscarriage	Pregnancy in right tube left hydrosalpinx	—
21	J. C.	33	5	Post partum pelvic inflammatory disease	Right hydrosalpinx left tubo-ovarian abscess	—
22	A. C.	34	13	Post-appendectomy peritonitis	Right tube and ovary previously removed left hydrosalpinx	Tube opened with air
23	A. T.	31	11	Post appendectomy peritonitis	Right tubo-ovarian abscess left hydrosalpinx	Tubes closed

*Three years later a total hysterectomy and bilateral salpingectomy were performed.

These tubes were difficult to operate upon, and patency was obtained in only 6 of this group. Such a poor result is probably due to the fact that gonorrheal infection has been shown to travel across the endometrium and endosalpinx and then to invade the deeper layers. Microscopical examination of the acutely inflamed tube shows why the damage is so extensive and why even years after

CASE REPORTS

CASE 1. V. K., a 31-year-old woman who had been married 8 years, had 2 living children — aged 7 and 5. She had lost 2 children at the ages of 3 and 8 months, and had had a miscarriage at 3 months. Severe puerperal fever developed 2½ years before the studies began. The infection subsided after 2 months' hospitalization and 3 months' rest at home. Conception failed to occur thereafter. Physical examination was negative except for a cervical laceration and a retroversion. Over an interval of months

three Rubin tests were done, and the tubes were found to be completely blocked. A uterosalpingogram showed the occlusion to be at the cornua. The husband had a normal physical examination and semen specimen. At operation the uterus was retrocessed, and there were numerous fibrous adhesions about both tubes. The tubes were patent and normal except for a fibrous, densely scarred portion at the junction of the tubes and the uterus. Resection of the cornua and implantation of the distal tube was done. A Rubin test 4 weeks postoperatively demonstrated the tubes to be wide open. The patient conceived 2 months postoperatively and

normal uterine cavity, but no filling of the tubes. The husband had a normal semen specimen. At operation she had many adhesions, and there was obliteration of both tubes at the cornua. The right tube was closed at the fimbriated end. This was opened. The cornua were excised bilaterally, and the tubes implanted into the uterus. Four weeks postoperatively the Rubin test demonstrated patency. A repeat test was equivocal, and a uterosalpingogram was unsatisfactory. The patient adopted a baby 18 months after operation and 1 month later conceived. She was delivered 9 months later by cesarean section.

TABLE 1 (Continued)

CASE No	RESULT OF UTERO-SALPINGOGRAM	TYPE OF OPERATION	RESULT OF RUBIN TEST POST OPERATIVELY	POSTOPERATIVE X-RAY STUDY	RESULT OF OPERATION
1	No oil left uterus	Implantation of both tubes	Tubes open	—	Pregnancy
2	Block at cornua	Implantation of both tubes	Tubes open	Right tube open left closed	Pregnancy 4 yr later
3	Block at cornua	Implantation	Tubes open	Equivocal	Pregnancy
4	—	Implantation of right tube and salpingostomy left salpingectomy	—	—	—
5	—	Fish-mouth plastic	—	Right tube patent	—
6	Tubes closed	Fish mouth plastic salpingostomy	Tubes closed	—	—
7	—	Bilateral salpingostomies	Tubes closed	Tubes closed	—
8	—	Bilateral salpingostomies	—	—	—
9	Bilateral hydro-salpinges	Bilateral salpingostomies	Tubes open	—	—
10	Left hydrosalpinx	Left salpingostomy	Tubes open	Tubes closed	—
11	Left hydrosalpinx	Right salpingectomy left salpingostomy	—	—	—
12	—	Bilateral salpingostomy	—	—	—
13	? patency films misread.	Bilateral salpingostomies	—	—	—
14	Both tubes blocked at cornua	Bilateral salpingostomies	Tubes closed	Tubes closed	—
15	Left hydrosalpinx	Salpingostomy myomectomy Estes operation	Tubes closed	—	—
16	—	Right salpingectomy left salpingostomy	Tubes closed	—	—
17	No filling of either tube	Lysis of adhesions and salpingostomy, bilateral tubal implantation	Tubes closed	No filling of either tube	—
18	—	Bilateral salpingostomies myomectomy	Tubes closed	Left tube freely patent	—*
19	—	Left salpingectomy right salpingostomy	—	—	—
20	—	Right salpingectomy left salpingostomy	Tubes closed	—	—
21	—	Right salpingostomy left salpingectomy	—	—	—
22	Left hydrosalpinx	Salpingostomy	Tube open	—	—
23	Bilateral hydrosalpinx	Salpingostomy	Tubes open	—	—

has been delivered. This patient obviously had an excellent prognosis since the cause of the block was definitely known and both she and her husband had previously been very fertile.

CASE 2 F G, a 30-year-old woman who had been married 2½ years had had no pregnancies. She had had pelvic peritonitis before her marriage, and a uterosalpingogram showed blocked tubes prior to the studies under consideration. Physical examination was negative. The Rubin test failed to demonstrate patency. Repeat x-ray studies showed a

CASE 3 R U, a 33-year-old woman, had been married 9 years, had had no pregnancies and had no history of pelvic inflammation. Her menstrual cycle was regular. Biopsy showed a secretory endometrium. Rubin tests failed to demonstrate tubal patency on repeated examinations. A uterosalpingogram showed both tubes blocked at the cornua by nodules suggestive of salpingitis isthmica nodosa. The husband had an excellent semen examination. At operation both tubes were blocked 19 cm from the fundus. The obstructed tubes were resected into the endometrial cavity, and the remaining patent tubes sutured into the uterus.

A Rubin test postoperatively demonstrated patency, and the patient experienced shoulder pain. A uterosalpingogram showed the right tube open and the left tube blocked. Four years later she conceived and had a normal delivery.

DISCUSSION

Before surgery is contemplated for treatment of tubal occlusion both husband and wife must be completely studied. The diagnosis of occlusion must be well established, preferably by both a Rubin test and a uterosalpingogram. There should be no history of tuberculosis, and the pelvic inflammatory disease, if present, should be in a chronic, quiescent stage, with no fever or leukocytosis. Observation over several months is indicated, during which conservative treatment is carried out. The woman should be otherwise in good health, with a negative physical examination. The husband must have been studied and must be fertile. After these studies operation for tubal occlusion can be recommended with full realization that success does not crown every effort. The gratitude of the patient who does become pregnant, however, affords impetus for further attempts.

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STREPTOMYCIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*

Review of the Literature and Report of a Case Caused by Bacteroides

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UP TO the present there have been scattered reports on the use of streptomycin in the treatment of subacute bacterial endocarditis. No individual series of cases has been large enough from which to draw conclusions. It is the purpose of this paper to present another unusual case of subacute bacterial endocarditis successfully treated with streptomycin, and to summarize the literature on the subject to May, 1949.

After several unencouraging reports, Loewe et al.,¹ 1944, showed that subacute bacterial endocarditis could be cured by penicillin given in sufficiently high doses for adequate lengths of time. Prior to this the prognosis in subacute bacterial endocarditis had been almost hopeless, subsequently the recovery rate has become approximately 80 per cent. In an effort to reduce further the 20 per cent failure rate other antibiotics have been sought for and tested. Since most of the failures are due to penicillin-resistant streptococci and to

gram-negative bacilli, both of which are often sensitive to streptomycin, this agent, next to penicillin, has proved most useful in the treatment of the disease. The first reports of streptomycin-treated subacute bacterial endocarditis appeared in 1946. In the ensuing three years and up until May, 1949, 49 cases treated wholly or partly with streptomycin have been reported in the literature.

REVIEW OF THE LITERATURE

Of the 49 cases, 28 were treated successfully. In the great majority of cases both penicillin and streptomycin were used. It was often difficult to attribute the successful outcome to either of the drugs or to a combination of both. In some cases it was possible to say that streptomycin was the decisive factor because of the progressively downhill course that had preceded its use.

Seventeen different organisms were encountered. There were 33 gram-positive organisms, of which 18 responded to treatment, and 18 gram-negative organisms, of which 12 responded to treatment. (In 2 cases² there were mixed infections.) In vitro

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sensitivity tests, although not completely dependable, can give a fair estimate of the prognosis but are not helpful in determining the dosage necessary for treatment. Thirty-eight organisms were tested for streptomycin sensitivity, 31 were found to be sensitive to 9 units or less per cubic centimeter, and of these, 21 were treated successfully. Seven were found to be sensitive to more than 9 units per cubic centimeter, and of these only 1 was treated successfully.

The range of streptomycin dosage varied widely. In some of the earlier cases small dosages for short periods were used because of the scarcity of the drug, and, remarkably enough, some of these patients recovered. In general the dosage used and the

that followed an unfavorable response to large doses of penicillin.

CASE REPORT

P. R., a 53-year-old waiter, was admitted to the New York Polyclinic Medical School and Hospital on December 2, 1947, because of increasing fatigue of 6 months' duration. Except for an occasional sore throat or pain in the knees he had been well until the previous July, when his remaining upper teeth had been extracted for replacement by a denture. Shortly after this he noticed increasing fatigue and weakness. Three weeks before admission he started to have fever, night sweats and chilly sensations, however, he continued to work. One week before admission he was forced to discontinue work because of weakness. He received seven daily injections of 300,000 units of penicillin in oil and wax without any appreciable effect on the fever, fatigue or night sweats.

Although he does not remember ever having had rheumatic fever, he knew that he had "murmurs of the heart" since

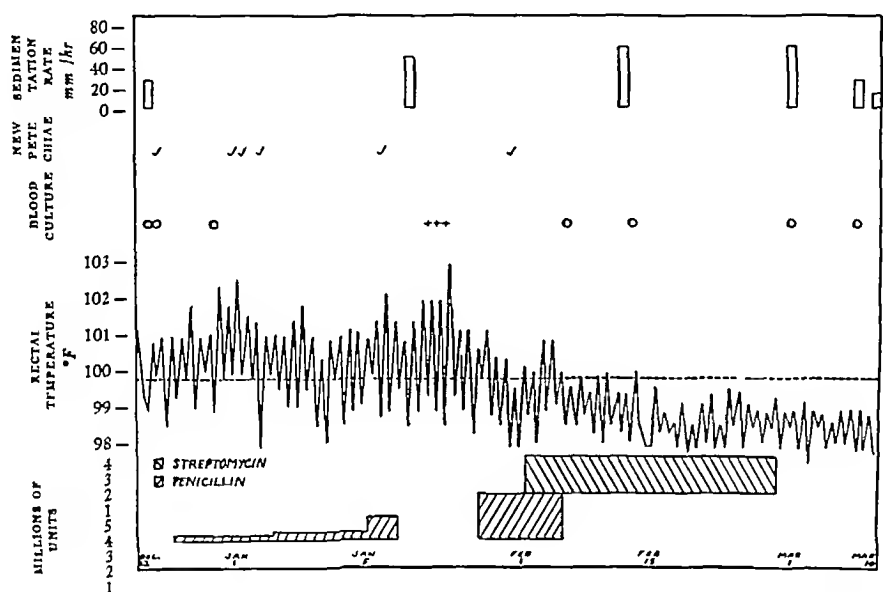


FIGURE 1 Effect of Streptomycin Therapy in a Case of Subacute Bacterial Endocarditis

length of time treatment was continued were less than that advocated for penicillin. This is fortunate because of the uniformity of appearance of toxic symptoms. In all the cases in which this was alluded to it was noted that such symptoms did appear and were frequently permanent. The decision when to discontinue streptomycin in the face of a favorable response and the appearance of toxic symptoms remains a difficult one. This is even more so because bacterial sensitivity to streptomycin decreases rapidly, unlike that to penicillin.

The pertinent features of these cases are summarized in Table 1.

An unusual case of subacute bacterial endocarditis is presented below because the causative organism, a bacteroid, is rare in endocarditis, and because of the favorable response to streptomycin

childhood. He had had malaria at the age of 12, a tonsilectomy at 49 and a submucous resection at 51 years of age.

Physical examination disclosed a well developed, fairly well nourished man of asthenic habitus. He appeared acutely ill. Close scrutiny of the skin and mucous membranes revealed no petechiae. The eyes, ears, nose, mouth and throat were normal except for the presence of an upper denture. The lungs were clear. The heart was enlarged, and the rhythm regular, and presystolic and systolic murmurs were heard at the apex. The liver and spleen were not palpable. The extremities were normal.

Examination of the blood showed a red-cell count of 3,650,000, with a hemoglobin of 72 per cent, and a white-cell count of 8000, with 65 per cent neutrophils, 34 per cent lymphocytes and 1 per cent eosinophils. Urinalysis was normal except for a faint trace of albumin, the sediment contained no red blood cells. The sedimentation rate (Westergren method) was 30 mm in 1 hour, and the icteric index was 10. Blood cultures taken on the 2nd, 3rd and 9th hospital days were negative. Urinalysis repeated on the 29th and 31st days demonstrated no red blood cells in the sediment. A roentgenogram of the chest showed emphysema of the lungs and a globular-shaped heart whose borders extended to the right and the left.

TABLE 1 Pertinent Features of Cases of Subacute Bacterial Endocarditis Reported in the Literature

CASE No	AUTHOR	AGE	SEX	ORGANISM	PENICILLIN SENSITIVITY	STREPTOMYCIN SENSITIVITY	PENICILLIN THERAPY	
					units/sec	units/sec	units	days
1	Priest & McGee ¹	36	M	<i>Streptococcus viridans</i>	0 8	0 1	500 000 1,000 000 1,500 000 2,000 000	35 42 28 —
2	Priest & McGee ¹	55	M	Nonhemolytic streptococcus	4 0	1 0	500 000 2,000 000	49 42
3	Priest & McGee ¹	42	M	Nonhemolytic streptococcus	6 0	1 0	1,000 000 2,000 000	28 9
4	Hunter & Duane ¹	40	M	Unidentified gram negative bacillus	—	3 75	500 000	3
5	Cady et al ¹¹	78	M	<i>Streptococcus faecalis</i>	Over 1 0	—	240 000	10
6	Hunter ⁷	57	M	<i>Pseudomonas aeruginosa</i> (<i>Bacillus pyocyaneus</i>)	—	15 0	—	—
7	Hunter ⁷	51	M	Unidentified gram negative bacillus	—	2 0	1 600 000	—
8	Hunter ⁷	49	M	Hemolytic streptococcus	3 0	8 0	5 000 000 10 000 000 10 000 000 4 000 000	12 14 14 28
9	Hunter ⁷	26	F	<i>Str faecalis</i>	8 0	3 5	—	—
10	Hunter ⁷	68	M	<i>Str viridans</i>	1 0	20 0	5 600 000 20 000 000	21 16
11	Hunter ⁷	—	—	Unidentified gram negative bacillus	—	1 0-16 0	—	—
12	Hunter ⁷	—	—	<i>Haemophilus influenzae</i>	—	1 5-2 0	—	—
13	Hunter ⁷	—	—	<i>Aerobacter aerogenes</i>	—	—	—	—
14	Hunter ⁷	—	—	<i>Ps aeruginosa</i>	—	40 0	—	—
15	Hunter ⁷	—	—	Unidentified gram-negative bacillus	—	7 0	—	—
16	Hunter ⁷	—	—	<i>Staphylococcus aureus</i>	10 0	0 4	—	—
17	Hunter ⁷	—	—	<i>Str viridans</i>	—	5 0	—	—
18	Hunter ⁷	—	—	<i>Str viridans</i>	—	5 0	—	—
19	Hunter ⁷	—	—	<i>Str viridans</i>	—	—	—	—
20	Hunter ⁷	—	—	<i>Str viridans</i>	—	—	—	—
21	Hunter ⁷	—	—	<i>Str faecalis</i>	—	4 0	—	—
22	Hunter ⁷	—	—	<i>Str faecalis</i>	—	—	—	—
23	Bland & Peterson ¹	32	F	<i>H para influenzae</i>	—	2 0	1 000 000	8
24	Appelbaum & Gelfand ¹	29	M	Gram negative bacillus of genus <i>Pasteurella</i>	Over 20 0	Over 25 0	200 000 800 000 300 000	1 4 3
25	Doret & Saegesser ¹⁰	26	M	<i>Str viridans</i>	50 times less than standard organism	—	109 000 000*	240
26	Wise & Miller ¹¹	31	M	<i>Pasteurella tularensis</i>	—	—	800 000	12
27	Solari et al ¹²	—	—	—	—	—	—	—
28	Muller et al ¹³	25	F	<i>Str viridans</i>	4 0	1 0	800 000 1 600 000 2 000 000 1 600 000 300 000	5 4 6 6 21
29	McGarvey & Ernstene ¹⁴	42	M	<i>Str viridans</i>	0 03	—	600 000 600 000 600 000 1 200 000 400 000	42 25 5 35 9
30	McGarvey & Ernstene ¹⁴	45	F	<i>Str viridans</i>	0 25	—	800 000 400 000	33 56
31	Olinger ²	26	M	<i>Str viridans</i> diphtheroids	0 02 0 1	0 6 8 0	800 000 2 400 000	—
32	Olinger ²	39	F	<i>Str viridans</i> <i>H para influenzae</i>	0 2 2 5	0 8 4 0	—	—
33	Massell et al ¹⁵	9	F	Gram negative coccobacillus (genus <i>Hemophilus</i>)	Over 10 0	—	—	—
34	Pearsall et al ¹⁶	31	F	<i>Str faecalis</i>	Complete resistance	3 0	12 000 000*	15
35	Pearsall et al ¹⁶	41	F	<i>Str viridans</i> (mitis strain)	Complete resistance	3 0	6 800 000*	17
36	Pearsall et al ¹⁶	19	F	<i>Str viridans</i> (mitis strain)	Complete resistance	3 0	8 000 000*	11
37	Guss ¹⁷	50	F	<i>Str faecalis</i>	Over 5 0	6 0	400 000 800 000 2 000 000 1 000 000 2 400 000	2 2 11 17 17
38	Clark et al ¹⁸	43	M	Nonhemolytic streptococcus	0 4	5 0	5 000 000 5 000 000 5 000 000 8 000 000	14 8 6 52
39	Rachmilewitz & Fried ¹⁹	18	M	<i>Str viridans</i>	0 2	9 0	—	—
40	McCoy & Meyer ²⁰	—	—	<i>Neisseria subflava</i>	—	0 5	—	—
41	McCoy & Meyer ²⁰	—	—	<i>Escherichia coli</i>	—	1000 0	—	—
42	McCoy & Meyer ²⁰	—	—	<i>H influenzae</i>	—	0 6	—	—
43	McCoy & Meyer ²⁰	—	—	<i>Corynebacterium</i>	1 0	5 0	0 8	—
44	Bell ²¹	31	F	<i>Str viridans</i>	—	—	0 8	15
45	DeMuth & Rawson ²²	40	M	<i>Ps aeruginosa</i>	Over 10 0	500 0	1 1	13
46	Cressy et al ²³	46	M	<i>Bacteroides</i>	—	—	10 0 0 4	5 31
47	Cressy et al ²³	75	M	<i>Str viridans</i>	3 0	100 0	1 2 210 000 000*	12 180
48	Stuart-Harris et al ²⁴	28	M	<i>Str viridans</i>	0 03	0 25	300 000 000*	150
49	Stuart-Harris et al ²⁴	34	F	<i>Str viridans</i>	Over 4 0	1 5	1 0	11
50	Leaman et al ²⁵	25	F	<i>Str faecalis</i>	1 25	—	4 0	66

*Total

TABLE I (Continued)

CASE No	STREPTOMYCIN THERAPY	days	RESULT	REMARKS
1	0 5	5	Death	Culture of heart valves at autopsy sterile streptomycin given just before death
2	0 5	21	Cure	Blood cultures remained positive after treatment with streptomycin was stopped but patient recovered and has been well for 9 mo cause of cure is questionable
3	0 5 0 2 0 4	11 42 17	Cure	Blood cultures positive before streptomycin was started cure can be attributed to streptomycin Follow up study for 6 mo
4	3 0	10	Cure	Sulfadiazine also given cure can be attributed to streptomycin Follow up study for 9 mo toxic febrile reaction to streptomycin
5	3 2 2 0	5 6	Death	—
6	3 0 4 0 6 0	14 5 7	Death	—
7	5 0	21	Cure	Cure can be attributed to streptomycin follow up study for 2 mo Toxic symptoms of dizziness and unsteady gait.
8	3 0	14	Death	—
9	4 0	28	Cure	Penicillin and streptomycin given concurrently follow up study for 10 mo Toxic symptoms of dizziness and unsteady gait.
10	6 0	7	Death	Resistance of organism to penicillin and streptomycin increased greatly during therapy
11	2 5	40	Death	Resistance of organism to streptomycin increased greatly during therapy vestibular and auditory toxic symptoms.
12	2 0	10	Cure	Penicillin and sulfadiazine also given cure can probably be attributed to combination of streptomycin and sulfadiazine.
13	2 0	7	Death	—
14	2 0-4 0	24	Death	—
15	2 6-3 2	20	Cure	Penicillin also given it is not possible to say which drug effected cure
16	1 5-3 0	26	Cure	Vestibular and auditory toxic symptoms
17	2 0	14	Death	—
18	3 0	34	Cure	Follow up study for 3 mo vestibular toxic symptoms.
19	5 0	1	Cure	Follow up study for 3 mo
20	1 0	15	Death	—
21	2 0 4 0 1 0-8 0	17 5 28	Death	3 mo remission between 2 courses of streptomycin resistance of organism to streptomycin increased greatly during second course toxic symptoms of fever and prostration
22	3 0	32	Death	—
23	2 4 4 2	3 10	Cure	Cure can be attributed to streptomycin toxic symptoms of vestibular and skin rash
24	1 5 4 0	13 14	Cure	Sulfadiazine also used follow-up study for 3½ mo cure can be attributed to streptomycin
25	1 0 3 0 2 0	1 6 6	Cure	Cure can be attributed to streptomycin
26	0 8	8	Cure	Diagnosis based on tick bite and positive agglutination test (1:200) blood cultures negative.
27	—	—	—	—
28	2 0	7	Death	Blood cultures positive before and negative after streptomycin was started patient died of congestive heart failure
29	4 0	5	Cure	Streptomycin given together with last course of penicillin blood culture positive before last course streptomycin decisive factor in this cure Follow-up study for 14 mo
30	4 0	7½	Cure	Streptomycin given together with last course of penicillin blood culture positive before last course streptomycin decisive factor in this cure.
31	2 0	6	Cure	Cultures negative and temperature normal when streptomycin was started effect of streptomycin doubtful
32	4 0	10	Cure	Penicillin and streptomycin given concurrently effect of streptomycin questionable follow up study for 1 yr
33	2 0	6½	Cure	Follow up study for 1 yr toxic febrile reaction
34	49 0*	23	Cure	Follow-up study for 1 yr cure attributed to streptomycin
35	36 0*	17	Cure	Follow-up study for 11 mo cure attributed to streptomycin
36	42 0*	19	Death	After streptomycin therapy was started patient improved and blood cultures became negative she died of subarachnoid hemorrhage
37	1 5 3 0	1 19	Cure	Follow-up study for 6 mo cure can be attributed to streptomycin toxic symptoms of dizziness and unsteady gait.
38	4 0 4 0 4 0	20 8 5	Cure	Cure attributed to penicillin
39	5 5	7½	Cure	Follow up study for 10 mo patient also received penicillin but cure was attributed to streptomycin
40	192 0*	52	Cure	Follow up study for 3 mo
41	22 0*	10	Death	—
42	48 0	24	Cure	Follow-up study for 10 mo
43	117 0*	42	Cure	Toxic symptom of skin rash
44	2 0	10	Cure	Follow up study for 18 mo
45	1 5	7	Death	4 abdominal operations in 8 mo bacteremia followed the last one
46	4 0	16	Cure	Follow up study for 3 mo toxic febrile reaction cure attributed to streptomycin
47	4 0	14	Death	Resistance of organism increased greatly during treatment.
48	72 5*	23	Cure	Failure for streptomycin cure attributed to penicillin and caronamide
49	34 5*	—	Cure	Failure for streptomycin cure attributed to penicillin and caronamide
50	4 0	10	Cure	Cure attributed to penicillin and caronamide

*Total.

The effect of streptomycin therapy is shown in Figure 1. On the 3rd hospital day two petechiae were found on the left buccal mucous membrane. On the 5th day penicillin, 500,000 units daily in divided doses every 3 hours, was begun. During the next 11 days the swinging temperature, night sweats and fatigue remained unchanged. New petechiae were found on three occasions, whereas the older ones faded. All were on the buccal mucosa. On the 16th day penicillin was increased to 800,000 units daily. For a few days the patient felt better and his appetite improved, but then he lapsed back to his previous state. On the 25th day the penicillin was increased to 2,400,000 units daily. On the next day two new petechiae appeared in the right conjunctiva, and one on the lower lip. Because it was believed that he was not making any progress, penicillin was discontinued on the 28th day.

Blood cultures were taken on the 32nd, 33rd and 34th days. After all therapy had been stopped the daily temperature spikes reached higher levels, and his general condition seemed to deteriorate more rapidly. On the 37th day it was believed that further delay might cause irreparable damage, and penicillin therapy was resumed, massive doses (5,000,000 units daily) being used. Although the temperature fell somewhat he remained otherwise unchanged and on the 41st day new petechiae appeared in the left conjunctiva. On the 42nd day the blood culture taken on the 32nd day was reported positive for bacteroids. Streptomycin, 4 gm daily in divided doses every 3 hours, was then started and continued for 28 days. Four days later, on the 46th day, the penicillin was discontinued. From the 45th day (3 days after the start of streptomycin therapy) clinical improvement was marked. His appetite improved, and he became more alert. From the 49th day the temperature remained below 100°F. No new petechiae appeared after streptomycin had been started. Two blood cultures taken after the beginning of streptomycin therapy (47th and 53rd days) and two after its termination (69th and 76th days) were negative. During the 3rd week of therapy symptoms of streptomycin toxicity appeared. The patient complained of dizziness, but his hearing remained unimpaired. The dizziness persisted for 6 months. When last seen in May, 1949, 14 months after discharge, he was in excellent health and working although he still had a slight gait disturbance.

DISCUSSION

The genus *Bacteroides*²⁶ is made up of gram-negative, obligate anaerobes, which are motile or nonmotile rods without endospores. They may or may not require enriched culture mediums. Until recently they comprised an amorphous unclassified group. They are normally inhabitants of the mucous membranes of the intestinal tract and may be found in the apical abscesses of teeth. They are rarely the cause of endocarditis. Four cases have appeared in the literature since 1945. Three²⁷ were treated with penicillin—2 successfully. The fourth²⁸ was treated with penicillin and streptomycin successfully, and the result attributed to streptomycin.

The organism isolated in the case reported above was found on three successive daily cultures. It was a minute gram-negative bacillus, which grew slowly and poorly on Kracke's blood culture medium. It also grew on Brewer's thioglycollate medium. It did not grow on blood agar under ordinary conditions but did grow sparsely on blood agar under 10 per cent carbon dioxide. Unfortunately, the organism died off before further bacteriologic studies or sensitivity tests could be done.

This man's illness most likely started with the extraction of his teeth six months before his admission. Penicillin in the amounts used inhibited

the organism (as evidenced by the persistently negative blood cultures during its administration) but could not effect a cure. After five days of penicillin in massive doses (5,000,000 units per day) the temperature receded somewhat, but new petechiae continued to appear and clinical improvement was not evident. It was not until seven days after streptomycin therapy that the temperature remained persistently below 100°F by rectum and clinical improvement was noted. Symptoms of streptomycin toxicity (vertigo) appeared during the third week and were very annoying for six months. The decision to continue streptomycin after the appearance of toxic symptoms was made because it was thought that this drug offered the only chance for recovery and because of the known loss of sensitivity that ensues when sublethal doses of streptomycin are used. When seen for follow-up examination fourteen months after discharge the patient had completely recovered and was able to work although he still had a mild gait disturbance.

SUMMARY

The literature relating to subacute bacterial endocarditis treated with streptomycin is reviewed.

A case of subacute bacterial endocarditis caused by *Bacteroides* and successfully treated with streptomycin is reported.

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EVALUATION OF TOLSEROL IN THE TREATMENT OF CHILDREN WITH CEREBRAL PALSY*

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THE basic concept of the treatment of cerebral palsy is re-education in the form of physical and occupational therapy. This treatment might be enhanced if a drug were found that would favorably influence the disabilities peculiar to this syndrome. This drug should have a relaxing effect on spastic and athetoid states and should facilitate the correction of resulting deformities. Since such a therapeutic program cannot be successful without the co-operation of the patient, the drug would be even more valuable if it were to alter favorably the child's attitude and behavior.

Tolserol (3-o-toloxv 1,2-propanediol) has been reported to effect relaxation¹ and to act favorably upon behavior.² Although its action is more dramatic when the drug is administered intravenously, Berger and Schwartz¹ have reported a beneficial relaxant effect on muscle spasm, spasticity and rigidity and an ameliorating effect on tremor and involuntary movement of extrapyramidal origin when the drug is given in adequate oral dosage.¹ Since the drug is relatively nontoxic in this form and is palatable, it makes an attractive pharmacologic approach to the treatment of cerebral palsy in children.

Any new drug proposed as an adjunct to such treatment should be rigidly evaluated prior to its release for general use. Therefore, a study of young children with cerebral palsy was initiated in the hope that this drug might help improve their condition.[†]

The purpose of this study is to evaluate the effect of tolserol on the child as a whole, as well as its specific action on the neuromuscular system. Inasmuch as many children with cerebral palsy fre-

quently make slow but steady developmental progress in their early years, a legitimate criterion for benefit from the drug should be a more marked quantifiable improvement over a relatively short period.

MATERIALS AND METHODS

Subjects

Sixteen children with ages ranging from three to eight years who had been attending the Meeting Street School for Cerebral Palsy from four to ten months were selected for study. Fourteen cases were diagnosed as spastic, 1 as athetoid, and 1 as ataxic. In classification of neuromuscular dysfunction, 2 were considered severe, 11 moderate, and 3 mild.||

Experimental Procedure

All the children had been attending the school for at least three months before the beginning of the drug evaluation. In the period prior to the beginning of the study, all the subjects were given complete pediatric, neurologic, orthopedic and psychologic examinations, as well as personality ratings by experienced nursery-school teachers.

The subjects were divided into two groups. Those in Group I received the drug for three weeks, followed by a placebo mixture for another six weeks, and then the drug was readministered for another three-week period. In Group II, the procedure was reversed: a placebo mixture was given for the first three weeks, after which the drug was substituted for six weeks, and the placebo was given again for the last three weeks. This procedure provided both a three-week and a six-week period of evaluation, and was of great convenience in statistical evaluation.

||A severe case was one in which the patient could not walk or utilize his hands with any degree of skill. A patient with a moderate case was one whose gait was decidedly deviant from normal and whose manual dexterity was impaired so that nursery school tasks were performed with difficulty. A mild case was one in which gait and manual dexterity were functionally good although lack of smoothness of movement was apparent.

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¶Tolserol was supplied through the courtesy of Dr. E. Sidney Newcomer, E. R. Squibb and Sons, New York City.

Medication

Tolserol was prepared with aqueous propylene glycol and syrup of cherry* so that 30 cc of the solution contained 10 gm of the drug¹. The dosage for each child was computed by Fried's rule based on a proportional amount according to body weight. The suggested adult dose was 10 gm three to five times daily¹. In this study the average dose was 33 mg per pound of body weight per twenty-four hours. The tolserol mixture was administered to each child six times a day. The group that was serving as a control (that is, patients receiving the placebo) in each period was given a menstruum that was similar to the liquid tolserol in ingredients, color, taste and smell but did not contain the drug. The medications were coded so that none of the staff or the parents knew in which drug period each child was actually receiving myanesin. Since each child attended school only three days each week, the medication had to be administered mainly at home. The parents of each child recorded each dose in a notebook. Occasional lapses in dosage were due to illness.

Methods of Evaluation

Neurologic examination consisted of evaluation of cranial nerves (third, fourth, sixth, seventh and eleventh), reflexes and tests for co-ordination (Romberg, diadokokinesis, gait and movements). Reflexes were graded on a nine-point scale from +4 (markedly hyperactive) through 0 (normal) to -4 (absent).

Orthopedic examination consisted of evaluation of the following points: ability to stand or walk, or both, deformities of gait, grasping functions of upper extremities and absence or presence (and degree) of spasticity and contractures of extremities and trunk. A physical therapist and an occupational therapist supplemented the orthopedic examination by weekly progress reports.

Psychomotor tests evaluated performance in fine manipulation and gross movement. Wallin pegboards A and B and the speed of placing ten marbles in a cup measured fine manipulation, whereas walking a measured distance (2½ yards) and up and down a flight of five stairs represented measures of gross bodily movement.

Personal-social rating scales were utilized to obtain objective measures of any behavioral changes. The records were completed by nursery-school teachers twice during each testing period. The nine items used rated sociability, activity control, noise-disturbance control, self-entertainment, co-operation in routine, work capacity, willingness to follow directions and mood swings. A similar rating scale was distributed to parents so that quantifiable data could be obtained of changes

observed in the home surroundings. In addition, a daily behavior chart was maintained by the nursery-school teachers to record any outstanding behavior not included in the rating scales.

Laboratory studies were performed to determine possible toxic effects on the hematopoietic and genitourinary systems, before and after each drug period. These tests consisted of blood counts and urine examinations.

Criteria of Improvement

The criteria of improvement due to drug action were considered to be a primary relaxing effect as shown by improvement in neuromuscular status and greater ease in motor performance, and a secondary effect on behavior because of neuromuscular relaxation, which might well be shown by lessened hyperactivity, greater concentration and more facile social relationships — characteristics that children with cerebral palsy frequently lack. Ratings of "improved" were judged as follows: neurologic — improved co-ordination, less hyperactive reflexes and improved function of areas innervated by the third, fourth, sixth, seventh and eleventh cranial nerves, orthopedic — decrease in deformity or improved function, or both, psychomotor — improved performance on five tests, and behavior — decreased irritability and hyperactivity, or increased sociability, or both. Ratings of "worse" were judged as follows: neurologic — poorer co-ordination, more hyperactive reflexes and greater cranial-nerve impairment, orthopedic — increased degree of deformity or increased impairment of function, or both, psychomotor — less accurate test performance, and behavior — increased irritability and hyperactivity or decreased sociability, or both.

RESULTS

There was no consistent outstanding, observable, over-all improvement in the children studied. One child improved in three of the methods of evaluation used, 7 improved in two, and 5 improved in one. On the other hand, 3 children showed no improvement or got worse in at least one category (Table 1).

Neurologic

Nine children (56.25 per cent) showed improvement. At the completion of the study, superficial and deep tendon reflexes were nearer normal, the Babinski reflex was lessened, and there was improvement in the Romberg sign and tests of co-ordination. Cranial-nerve action did not seem to be affected. Six children (37.5 per cent) became worse, and 1 (6.25 per cent) showed no change.

Orthopedic

Five children (31.25 per cent) showed slight improvement. In no case was a striking improvement

*Tolserol 80 propylene glycol 480 camphor water 720 distilled water 720 and syrup of cherry as needed 2400

noted Two patients (12.5 per cent) became worse, and in 9 (56.25 per cent) there was no change

Psychomotor

Five children (31.25 per cent) improved, 2 (12.5 per cent) became worse, and 9 (56.25 per cent) showed no change. Statistical analysis of group results demonstrated no significant difference between the group while the drug was being given and the group while the placebo was being given. All tests for fine motor co-ordination showed a slightly longer mean performance time, whereas tests for gross

or later. Whether this was because insufficient dosage of the drug was given or because the clinical methods of testing behavior were not sufficiently sensitive to reflect minimal degree of improvement is difficult to state.

It has been the experience with curare, which has also been used to facilitate relaxation in cerebral palsy, that the degree of orthopedic improvement, when it occurs, is measurable, even though the effect may be transient.³ With tolserol, this grossly relaxant effect was observed neither by the orthopedic surgeon in his examinations nor by

TABLE 1 Pertinent Data and Summary of Results in 16 Children Who Received Tolserol

CASE No	AGE		DIAGNOSIS	DEGREE	DOSE gm./24 hr	RESULTS			
	yr	mo				NEUROLOGIC	ORTHOPEDIC	PSYCHOLOGIC	BEHAVIOR
1	3	3	Spastic diplegia	Moderate	1.3	Improvement	No change	No change	No change
2	2	8	Spastic diplegia	Moderate	0.96	Patient worse	Slight improvement	Slight improvement	No change
3	3	5	Spastic diplegia	Mild	0.96	Improvement	Slight improvement	Slight improvement	No change
4	5	7	Spastic monoplegia	Moderate	1.0	Improvement	No change	No change	Improvement
5	3	8	Spastic hemiplegia	Moderate	1.2	Patient worse	No change	No change	No change
6	4	8	Spastic hemiplegia	Moderate	1.4	No change	No change	Slight improvement	Improvement
7	4	6	Spastic hemiplegia	Moderate	1.3	Improvement	Patient worse	Patient worse	No change
8	3	3	Spastic hemiplegia	Moderate	1.2	Improvement	No change	No change	Improvement
9	4	1	Spastic hemiplegia	Mild	1.0	Improvement	Slight improvement	No change	No change
10	6	1	Spastic hemiplegia	Mild	1.9	Patient worse	No change	No change	Patient worse
11	3	2	Spastic quadriplegia	Moderate	1.1	Improvement	No change	No change	No change
12	3	7	Spastic quadriplegia	Moderate	1.2	Improvement	No change	Improvement	No change
13	8	6	Spastic quadriplegia	Severe	1.6	Patient worse	Patient worse	Patient worse	No change
14	6	6	Spastic quadriplegia	Severe	1.1	Patient worse	Slight improvement	No change	Patient worse
15	6	6	Athetosis	Moderate	1.4	Patient worse	No change	No change	No change
16	5	9	Ataxia	Moderate	1.3	Improvement	Slight improvement	Slight improvement	Patient worse

bodily movement showed a slightly faster mean performance time — neither significantly so, however.

Behavior

Three children (18.75 per cent) improved, 3 (18.75 per cent) became worse, and the remainder showed no changes in over-all behavior. More specifically, 7 children showed improvement in one but not more than two of the personal-social behavior items, whereas 6 were reported as worse in one or two items, and 3 showed no change. The behavior items affected were usually sociability, self-entertainment, elation and depression.

Laboratory Studies

There were no significant deviations from the normal in urine or blood counts either during administration of the drug or after the cessation of tolserol therapy.

DISCUSSION

The results of this study proved interesting in several respects. Although there were no outstanding general improvements, there was evidence that the drug caused a diminution of exaggerated reflexes and some improvement in co-ordination. These results are in accord with those reported by Berger and Schwartz¹ and Gammon and Churchill.² However, this change in neurologic status did not seem to be reflected in improved over-all performance or in improved relaxation either immediately

the physical therapist in her tri-weekly therapeutic periods. Thus, although in 5 cases there was improvement from the orthopedic standpoint, the improvement was invariably slight and not of appreciable degree in any case. It is also of note that in 2 cases (12.5 per cent) the patients became definitely worse orthopedically while on tolserol therapy.

Performance time on tests of fine manipulation tended to be slightly slower on the drug, whereas in tests for gross bodily movement the time was somewhat faster. However, in neither case were the results statistically different from those of the control group.

Since it is recognized that parents and workers tend to be overly enthusiastic when they know a new drug is being administered, this study was designed to evaluate behavioral results of tolserol as objectively as possible and to minimize unwarranted conclusions based on subjective opinion alone. Nevertheless, great leeway was given both parents and nursery-school observers to report noticeable behavior changes in any way, and at the same time reports on objective behavior scales were required. In spite of the natural inclination for enthusiasm, in only 3 children could improved behavior be noted in the drug periods. Favorable behavioral changes might be expected, since one might assume that when a spastic child is relaxed he would feel happier or "lighter," a result obtained with a comparable group studied with curare.⁴

Three children who had been reluctant to participate in group activities for several months prior to administration did seem happier during the drug administration. On the other hand, a similar number of children became gloomy or withdrawn when they received the drug.

A liquid vehicle for administration is preferred since it has been shown experimentally that a higher drug concentration is obtained by this method and that absorption is much more uniform than by tablets.⁵ The drug was given six times a day at two-hour intervals to ensure maximum concentration in the blood for at least twelve hours a day during each entire three-week period of administration. There were no observable toxic effects, although for the first few days a few children complained of nausea and abdominal pain. This effect was transient.

It is believed that the drug did not have a primary or secondary relaxing effect. It did have a specific beneficial relaxant effect on some children as shown by improved reflexes only, but improved behavior and performance were negligible. The methods utilized in this study were considered sufficiently sensitive to demonstrate any improvements had they been present. It is possible that the dosage was not sufficient to achieve adequate relaxation although the dosages employed were of the same relative magnitude as those recommended in the literature.¹ If this is so, further study should be

initiated to ascertain the maximum dosage that can be tolerated in children of this age.

SUMMARY

Sixteen children with cerebral palsy received tolserol in two three-week periods. No definite over-all improvement was noted.

Improvement was primarily in the neurologic category. 56.25 per cent of the children showed diminution of exaggerated reflexes, and 12.5 per cent became worse.

Orthopedic improvements were slight. Five patients (31.25 per cent) showed improvement, not marked, and 2 (12.5 per cent) became worse, 9 (56.25 per cent) showing no change.

Locomotion was improved somewhat in 6 cases (37.5 per cent).

Behavior changes were not appreciable.

The drug did not produce any noticeable toxic effects.

We are indebted to the staff and consultants of the Meeting Street School for their invaluable assistance in this research.

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ORAL ADMINISTRATION OF AUREOMYCIN IN THE TREATMENT OF URINARY INFECTIONS*

ALEXANDER M. RUTENBURG, M.D.,† AND FRITZ B. SCHWEINBURG, M.D.‡

BOSTON

IN A previous communication¹ intramuscular injection of aureomycin hydrochloride was reported to be not only a highly effective antibiotic in a variety of urinary infections but also, in many cases, curative after other antibiotics had failed. Owing to the pain caused by the intramuscular injections, even when the drug is given in a 1 or 2 per cent procaine solution, a subsequent series of 26 patients were treated by aureomycin given orally.

OBSERVATIONS

These cases comprised an unselected group of 26 acute and chronic urinary infections and included 5 with chronic renal insufficiency. Seventeen patients had had prior treatment with other anti-

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biotics without clinical or bacteriologic improvement. Twenty had one or more of the following complications: hydronephrosis, calculi, ureteral stricture and prostatic obstruction. Obstructive disease, if present, was treated during aureomycin therapy.

Twenty-one of the infections were due to a single organism, and 5 to more than one. The organisms involved were *Escherichia coli* (8 cases), *Aerobacter aerogenes* (12 cases), *Pseudomonas aeruginosa* (11 cases), *Proteus vulgaris* (1 case), hemolytic *Staphylococcus aureus* (1 case) and *Streptococcus faecalis* (1 case).

Two grams of aureomycin was given daily in divided doses for four to six days, or longer, so long as bacteria were present. If cure did not result in two weeks, the drug was discontinued.

Oral administration of aureomycin was generally well tolerated. In 3 patients with nausea and another with diarrhea, the reactions were mild, and the therapy was not interrupted. In 2 other patients

vomiting prevented oral therapy, and the drug was given parenterally. The reactions varied with different lots of the drug. With the more recent lots, no gastrointestinal symptoms occurred. Renal injury was not observed during treatment. The nonprotein nitrogen was not increased in patients with renal insufficiency. Shortly after the drug had been started the urinary pH dropped to 4.5 to 6.0 and remained within this range as long as the drug was administered. Catheter specimens were cultured every second day, and treatment was continued for two or three days after the first sterile specimen. The patients were followed for ten to thirty days and were considered cured only when two to five specimens of urine were found to be sterile after cessation of treatment. Anemia, leukopenia or thrombopenia did not develop. The white-cell counts, which had been elevated before treatment, dropped to normal values within one or two days when treatment was successful.

RESULTS

The clinical symptoms disappeared in all patients in a surprisingly short period—usually within twenty-four to forty-eight hours. It is noteworthy that the clinical improvement occurred whether the urine had or had not become sterile. In cases in which bacteria persisted, the clinical symptoms usually recurred when the drug was discontinued. The urine became sterile in 16 cases and remained so after the drug was discontinued.

A close correlation was observed between the clinical result and the *in vitro* sensitivity of the organism to aureomycin. Thus, a rapid cure of the infection was obtained in every case in which the strain was sensitive, whereas partial or total therapeutic failure resulted when the strain was resistant.

The sensitivity of bacteria to a given antibiotic varies considerably, not only from species to species but also from strain to strain within a species. One hundred and thirty strains of various species, including many of those encountered in the present group of cases, were tested for sensitivity *in vitro* to aureomycin by the serial tube-dilution method.¹ This method tests the response of a twenty-four-hour broth culture inoculated with some 20,000 organisms of a particular strain to graded dilutions of the antibiotic. The lowest concentration of an antibiotic, in microgm per cubic centimeter, that produces no macroscopically visible growth after incubation for twenty-four hours at 37°C is considered the bactericidal titer. This titer for aureomycin was found to be as follows: the titer for thirty-five strains of *Ps aeruginosa* varied from more than 200 to 0.0125 microgm per cubic centimeter, over half the strains requiring more than 50 microgm per cubic centimeter. The titer for thirty strains of *P vulgaris* ranged from over 200 to 0.0125, a third of the strains requiring more than

50 microgm per cubic centimeter. The titer of twenty-five strains of *Esch coli* and of twenty strains of *A aerogenes* ranged from 6.25 to 0.0125 microgm per cubic centimeter, but with an occasional strain requiring more than 200. The titer of ten strains of hemolytic *Staph aureus* and of ten strains of beta-hemolytic streptococcus were inhibited by 0.4 to 0.0125 microgm per cubic centimeter. If the growth of a strain was completely inhibited by a concentration of less than 50 microgm of aureomycin per cubic centimeter of culture, the strain was considered sensitive. If the growth was completely inhibited by a concentration of 50 microgm or higher per cubic centimeter of culture, the strain was considered resistant.

There was recurrence of infection in 2 patients. The first had chronic urinary retention and acute pyelonephritis due to *A aerogenes* that was very sensitive to aureomycin *in vitro*. He responded rapidly to aureomycin therapy, but twice at intervals of three weeks the infection recurred. Both relapses yielded promptly to the drug.

The second patient, with severe cardiovascular disease, renal tumor and a hypertrophied obstructing prostate, had an infection due to *Ps aeruginosa* that was very sensitive to aureomycin *in vitro*. Twenty days after the drug had been discontinued the infection recurred and again responded rapidly to the drug.

In a third patient with chronic cystitis and pyelonephritis due to *Esch coli*, as well as renal insufficiency and a blood nonprotein nitrogen varying from 80 to 120 mg per 100 cc, the infection was cured within forty-eight hours. The urine remained sterile for twenty-eight days. Reinfection occurred with *A aerogenes*. A second course of therapy promptly sterilized the urine, which remained sterile for the next fourteen weeks, when observation was discontinued.

In these 3 patients, bacterial resistance to aureomycin did not develop.

A fourth patient, with a vesicovaginal fistula and a mixed urinary infection due to *A aerogenes*, *Str faecalis* and *Ps aeruginosa*, improved clinically, but only the first two of these organisms were cleared from the urine. *Ps aeruginosa* remained. In a fifth patient with mixed infection, one organism (*A aerogenes*) was cleared, but the other (*Ps aeruginosa*) was not. This patient also showed clinical improvement.

There were 5 bacteriologic failures in monovalent infections, 1 due to *Esch coli* and 4 to *Ps aeruginosa*. In these cases the bacteria were resistant to aureomycin *in vitro*.

Of 34 strains of bacteria found in the urines of the 26 patients, all 12 strains of *A aerogenes*, 7 or 8 strains of *Esch coli* and 1 strain each of *P vulgaris*, hemolytic *Staph aureus* and *Str faecalis*, were eliminated from the urine. Of 11 strains of *Ps aeruginosa*, 5 that were sensitive to the drug

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in part in such conditions as hereditary hemorrhagic telangiectasia scurvy and hemophilia conditions associated with extreme thrombocytopenia hypoprothrombinemia and fibrinogenopenia and conditions associated with circulating anticoagulants and other abnormalities (Table 1)* In other cases it is possible to indicate the abnormal mechanism responsible for bleeding such as thrombocytopenia even though the biologic effect of the abnormality may not be completely understood and the cause of thrombocytopenia may not be evident Certain aspects of these tests are arbitrary nonspecific, crude, poorly defined and limited in significance by a lack of understanding of some features of their mechanism Also there may be a lack of true correlation of certain results obtained in vitro with the symptoms and signs observed in vivo For example there may be thrombocytopenia with or without hemorrhagic diathesis in hemophilia bleeding may continue in a serious degree when the clotting time, as measured in glass tubes has returned toward normal

HYPOTHESES CONCERNING HEMOSTASIS IN NORMAL SUBJECTS

Hemostasis is a term that by definition means halting the escape of blood Hemostasis probably results from a combined effect of extravascular factors, such as location of the vessel and tone of the surrounding tissue, vascular factors, such as size and structure of the vessels as well as vascular tone, and factors of clot formation such as the number of platelets and the amounts and state of the constituents of the blood required for proper blood coagulation A defect in any one of these three factors may result in an alteration of hemostasis In hemorrhagic diathesis, consideration is too often limited to the coagulation of blood itself All three of the factors listed above must be considered and critically scrutinized when bleeding is not halted spontaneously The critical reports of Quick,¹ Macfarlane,² Tocantins,³ Zucker⁴ and Zucker⁵ contain detailed discussions of the experimental evidence and the hypotheses concerning hemostasis in the normal person and the alterations observed in disease The theory of blood coagulation is discussed below

In the normal subject, hemostasis following injury occurs spontaneously, presumably because of the following series of mechanisms which are here outlined in an oversimplified manner More detail is given in the sections describing special tests

Extra-vascular Factors

When bleeding occurs from a vessel such as a capillary, the hydrostatic pressure within the vessel falls and that in the surrounding tissue rises as a

*Deficiency of calcium of sufficient degree to interfere with the clotting mechanism is not compatible with life Accordingly hypocalcemia is not observed clinically as a cause of hemorrhagic disease.

result of the outflow of blood from the ruptured vessel The increase in tissue pressure in combination with normal tissue tone tends to reduce the flow of blood through as well as from the ruptured vessel

Vascular Factors

After vascular rupture vasoconstriction and retraction of the vessel promptly occur Vasoconstriction lasts for a few minutes or a longer period tending thereby to occlude the lumen of the vessel Retraction also tends to occlude the lumen by mechanically blocking the opening of the vessel by means of the surrounding tissue

Factors of Clot Formation

Concomitantly with rupture of a vessel blood escapes into the surrounding tissue and may be mixed with tissue factors that enhance clot formation In the lumen of a ruptured vessel itself platelets agglutinate and adhere to the area of broken intima Fibrin is deposited about the platelets that disintegrate This apparently enhances the formation of a clot, with subsequent retraction, so as to form a plug in the lumen of the vessel If the clot formation is secure, hemostasis continues after the vessel is no longer constricted The clot will then be organized or resolved with recanalization of the vessel

DIAGNOSTIC PROCEDURES FOR THE STUDY OF PATIENTS WITH HEMORRHAGIC DISEASES

It is recommended that the physician study a patient with hemorrhagic disease by means of a systematic approach from the basic and screening examinations to the more specialized tests, certain of which are discussed below in detail

Basic and Screening Examinations

These include history physical examination, basic examination of the blood (determination of hemoglobin or hematocrit, white-cell count and differential count, estimation of the number of platelets from the stained smear and serologic test for syphilis), basic examination of the urine and basic examination of the stool From the initial study of the patient, a presumptive diagnosis can be made in certain cases of a disease complicated by hemorrhagic manifestations or of a primary hemorrhagic disease The vascular defense and the process of clot formation are usually studied to aid further in diagnosis

Special Tests Related to Vascular Defense and Clot Formation

Vascular defense and clot formation are determined by the following procedures measurement of capillary fragility, bleeding time, platelet count, clot retraction, coagulation time, clotting time of recalcified plasma, screening tests for abnormal

in vitro were eliminated, whereas 6 that were resistant in vitro were not

DISCUSSION

Sixteen of 26 patients were promptly cured by a single course of oral administration of aureomycin. Several courses were required in the 3 patients who had recurrence of infection. In these and in the patient with a vesicovaginal fistula, the underlying disease had not been dealt with successfully. Clinical improvement resulted in all the patients in this series, even in the 7 cases of failure to eradicate the bacteria (1 of *Esch coli* and 6 of *Ps aeruginosa*). There was exact correlation between bacterial sensitivity in vitro and the immediate bacteriologic response, regardless of whether the complicating disease was dealt with successfully. In the latter cases recurrences or reinfections were to be expected, and in fact occurred. Such patients cannot be permanently cured by any antibiotic. These results in *Ps aeruginosa* infections are better than those reported by others.^{2, 3} In 2 cases the strains that were resistant to aureomycin yielded to subsequent treatment with sulfamethazine⁴ to which they were very sensitive in vitro. We have

observed no case in which bacterial resistance to the drug developed during treatment.

SUMMARY

In 26 patients with a variety of urinary infections, due chiefly to gram-negative bacilli, aureomycin was as effective by oral as by intramuscular administration. Clinical improvement occurred in all cases. Bacteriologically, 19 patients, of whom 12 had failed to respond to other antibiotics and 13 had complicating disease in the urinary tract, were cured, 16 by a single course and 3 by repeated courses of therapy. *Pseudomonas aeruginosa* was the least susceptible of the bacteria encountered. Bacterial resistance did not develop.

We are indebted to Miss Annette Freedman for technical assistance.

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MEDICAL PROGRESS

HEMORRHAGIC DISEASES*

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THE subject of hemorrhagic disease is considered under the general headings of problem in diagnosis, hypotheses concerning hemostasis in normal subjects, diagnostic procedures, history, physical examination, basic examination of blood, urine and stool, measurement of capillary fragility, bleeding time, platelet count, clot retraction, measurement of coagulation and clotting times of venous blood, clotting time of recalcified plasma, screening tests for abnormal coagulation, determination of prothrombin activity, prothrombin consumption and determination of fibrinolysis.

PROBLEM IN DIAGNOSIS

The physician is called upon to diagnose and treat patients with signs and symptoms of an in-

creased tendency to bleed. The manifestations of hemorrhagic diathesis are extremely variable, since abnormal bleeding may be evidenced as purpura in the skin, subcutaneous hemorrhage, bleeding from any mucous surface or hemorrhage into any structure or organ of the body.

Since the prognosis and treatment for the patient with hemorrhagic diathesis vary widely, it is essential to establish, as well as possible, the diagnosis or mechanism for the bleeding. This is done by at least two approaches. In the first place the patient is studied, a series of basic and screening examinations being used, in an attempt to establish a diagnosis of the primary illness, which may or may not be that of a primary hemorrhagic disease. Secondly, a series of special examinations of a biologic nature are made to evaluate qualitatively and quantitatively abnormalities of the vascular defense of the body and of the process of clot formation.

With these data, the underlying disease and the mechanism causing hemorrhage can be defined.

*Adapted from *A Syllabus of Laboratory Examinations for Clinical Diagnosis* (in press) by permission of the Harvard University Press.

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TABLE 1 (Continued)

DISEASE	COMMENTS ON MECHANISM	BLEEDING TIME	COAGULATION TIME	CLOT RETRACTION	PLATELET COUNT	TOURNIQUET TEST	PROTHROMBIN CONCENTRATION	PROTHROMBIN CONSUMPTION
Hemorrhagic disease associated with <i>thrombocytopenia</i> <i>poor clot retraction and increased capillary fragility*</i>								
Purpura hemorrhagica idiopathic thrombocytopenic purpura (Werlhof's disease) thrombocytopenia with variable degrees of abnormality of capillaries	Mechanism of bleeding in this disease is known only in part. coagulation defect is associated with deficiency of 'platelet enzyme' there is poor clot retraction with decrease in adhesiveness rigidity and contractility and there is apparent failure to form platelet plug in severed vessel. The vascular defect is poorly understood. This disease occurs in children in adults it occurs largely in young women occasionally in men. It is of undetermined origin may be acute or chronic and is associated with variable degrees of thrombocytopenia, purpura and ecchymosis. Spontaneous recovery may occur in acute adolescent cases. In chronic type splenectomy may give symptomatic cure in about 70 per cent of cases in spite of continuing thrombocytopenia occurring in many cases. Diagnosis requires excluding causes of "secondary" thrombocytopenia.	Usually prolonged	Normal	Poor	Decreased	Marked increase in capillary fragility	Normal	Poor
Secondary' or symptomatic thrombocytopenic purpura (thrombocytopenia with variable degrees of abnormality of capillaries)	Mechanism of bleeding is the same as that in purpura hemorrhagica. It is acute or chronic hemorrhagic disease with symptoms and signs similar to those of idiopathic thrombocytopenia and may occur in children and adults of both sexes. Thrombocytopenia may be associated with such conditions as invasion of bone marrow (myelophthisis) aplastic marrow irradiation drug intoxication as with benzol allergic response as possibly illustrated by sensitivity to organic arsenical drugs. Sedormid and sulfonamides following thermal burns nutritional deficiency in pernicious anemia and occasionally with uremia.	Usually prolonged (may show great variation)	Normal	Poor	Decreased (may show great variation)	Marked increase in capillary fragility (may show great variation)	Normal	Poor (may show great variation)
Hemorrhagic diseases associated with manifest <i>abnormalities of clot formation</i>								
Hypoprothrombinemia	Mechanism of bleeding is impaired blood coagulation.	May be increased in severe cases	May be increased in severe cases	Normal†	Normal	Capillary fragility may be increased in severe cases	Decreased (usually only defect)	Normal
Lack of prothrombin or presence of antiprothrombin substance administered such as Dicumarol	Hypoprothrombinemia may be associated with severe hemorrhagic disease as evidenced by purpura ecchymoses and bleeding into any tissue. Hypoprothrombinemia may occur in such conditions as congenital absence (rare) faulty absorption of vitamin K as in absence of bile salts and in melena neonatorum steatorrhea or diarrhea defective formation by diseased liver and administration of Dicumarol and large doses of salicylates. Vitamin K, administered parenterally, usually restores prothrombin if there is adequate liver function. Massive doses may be needed after Dicumarol therapy.							
Circulating anti-coagulants (heparin and other anticoagulants)	Bleeding results from inhibition of coagulation by anticoagulants circulating in blood stream in such conditions as administration of heparin and ionizing doses of irradiation probably due to heparinemia. In other cases type of anticoagulant has not been classified.	Normal	Prolonged (patient's plasma may prolong clotting time of normal plasma or whole blood)	Normal	Normal	Normal	Normal	No studies reported

*Relation between thrombocytopenia and capillary fragility is not known

†Clotting time of whole blood not reliable index of degree of hypoprothrombinemia

TABLE 1 *Classification of Hemorrhagic Diseases, with Comments on Mechanism and Certain Laboratory Tests*

DISEASE	COMMENTS ON MECHANISM	BLEEDING TIME	COAGULATION TIME	CLOT RETRACTION	PLATELET COUNT	TOURNIQUET TEST	PRO-THROMBIN CONCENTRATION	PAO-THROMBIN CONSUMPTION
Hemorrhagic diseases associated with apparent abnormalities of vascular bed but with normal platelets and essentially normal blood coagulation								
Hereditary hemorrhagic telangiectasia (Rendu Osler, Weher disease)	Non sex-linked hereditary disease exhibiting telangiectatic lesions consisting of thin-walled dilated capillaries that are exposed and may bleed from slight trauma. Some capillaries show wall consisting of endothelium only with complete loss of supporting elastic tissue. Others reveal complete vascular wall with dilatation and exposure as only abnormalities. There are usually no symptoms in childhood; symptoms occur with increasing age in adults. Lesions may be located on skin or mucous membrane or in viscera. Patients may have no hemorrhage. Intermittent hemorrhage may occur externally or internally. There is no specific treatment.	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Localized areas of exposed thin-walled capillaries								
"Thrombasthenia" hereditary hemorrhagic diathesis pseudohemophilia (von Willebrand and Glanzman)	Mechanism of bleeding is unknown but may be related to abnormal function of platelets or vascular malfunction such as poor vascular constriction following injury. Disorder may be familial and transmitted to either sex. There occurs persistent bleeding following minor trauma, bleeding gums, ecchymoses, melena, hematuria, epistaxis and in females menorrhagia and metrorrhagia. Hemarthroses have been reported but are rare. It is not known whether these cases represent disease entity or several diseases. There is no known treatment.	Markedly prolonged for normal	Prolonged in some cases	May be reduced	Normal	Increased capillary fragility in about 50% of cases	Normal	No studies reported
Scurvy (decreased intercellular collagen substance)	Hemorrhage appears to result from lack of intercellular collagen substance due to prolonged deficiency in ascorbic acid and may be associated with purpura that is perifollicular or there may be large ecchymoses.	Normal	Normal	Normal	Normal	Marked increase in capillary fragility, but test returns to normal promptly after administration of vitamin C	Normal	Normal
Senile purpura (lack of supporting structures)	Rupture of capillaries presumably results owing to loss of elasticity and atrophy of supporting tissues. In senility it is not uncommon for purpura and hematomas to develop especially in dependent parts of body with or without trauma.	May be slightly prolonged	Normal	Normal	Normal	Capillary fragility may be slightly increased	Normal	Normal
Sepsis (increased capillary fragility of toxic origin)	Although mechanism is unknown it is thought that purpura results from defect in capillary wall probably on toxic basis. Purpura may occur with or without septic emboli to capillaries of skin.	Normal	Normal	Normal	Normal	Capillary fragility may be increased	Normal	Normal
Allergic purpura (Henoch's and Schönlein's purpura) abnormal response of capillaries	Bleeding results from increased capillary permeability with resultant passage of plasma and blood cells through capillary wall. Such increased permeability is probably of allergic origin (drug intoxication, food idiosyncrasies and certain infections). Purpura joint symptoms and fever were described by Schönlein. Visceral lesions may occur including those of bowel (Henoch's purpura). Diagnosis usually made by exclusion of other causes for purpura and by associated symptoms and signs of primary abnormality.	Normal	Normal	Normal	Normal	May be normal or may show increased capillary fragility	Normal	Normal

Classification of Hemorrhagic Diseases

A brief classification of hemorrhagic diseases, based on known abnormalities and changes in certain tests for hemorrhagic diathesis, is presented in Table 1. Such a table is necessarily incomplete and oversimplified, more complete discussions of the diseases and their physiologic causes have been given elsewhere.^{1-3 6-67}

HISTORY

A complete and critical history is of first importance in the diagnosis of the cause of hemorrhagic diathesis. Often, the history alone provides adequate data on which to base a presumptive diagnosis. The history of abnormal bleeding occurring in alternate generations in male members of a family is presumptive evidence for the diagnosis of hemophilia. The history of familial bleeding that is not sex-linked suggests the possibility of "thrombasthenia." One may best obtain the *family history* by setting up a family tree on paper and, together with the patient and other members of the family, discussing and determining hemorrhagic diatheses in each member of the family as far ancestrally as is known. Often, it is necessary to question the patient and relatives to determine the onset and characteristics of bleeding. It is of importance to know the age of the patient at the *onset of bleeding*. An acute episode frequently brings the patient to the physician, but the past history will reveal many episodes of bleeding tendency reflected in such observations as frequent epistaxis, easy bruising, menorrhagia, metrorrhagia, hemarthrosis simulating arthritis, bleeding with eruption of deciduous and permanent teeth and severe hemorrhage with minor surgical procedures, such as circumcision, tonsillectomy and tooth extractions. The relation of bleeding at time of menses should be carefully investigated, since exaggeration of the normal menstrual bleeding may serve as an important index of a hemorrhagic diathesis. It is of importance to determine whether the patient has been exposed to potentially harmful drugs, chemicals or physical agents. The presence of infection, allergic symptoms or other diseases such as anemia is investigated historically in the patient. A dietary history may reveal an inadequate intake of vitamin C over a prolonged period and may thus suggest the diagnosis of scurvy.

PHYSICAL EXAMINATION

Usually, the physical signs occurring in hemorrhagic diseases do not permit a specific diagnosis to be made. The physical signs will depend on the site of hemorrhage. In *familial telangiectasia*, the lesions may be seen in the skin and mucous membranes.²⁴ In *purpura** petechiae may predominate

*Purpura is not a disease entity but a physical sign. Purpura means literally a purple effluvia from which a purple dye was extracted.

in dependent portions of the body and may be associated with bleeding of the mucous membranes. Intracranial hemorrhage may be manifested by signs of hemiplegia but there may be little evidence of hemorrhage elsewhere in the body. The follicular and perifollicular purpura of *scurvy* may be associated with massive hemorrhage into muscles and subcutaneous tissues without hemarthrosis.

In *hemophilia*, the occurrence of hemarthrosis is frequent enough to suggest the diagnosis. However, at any one time, there may be only one site of bleeding, such as hematuria, or there may be bleeding into more than one joint or into skin, muscle, mucous membranes or viscera.

The *complications of hemorrhage* may include the following: loss of large amounts of blood, pain and swelling, pressure from hematomas with obstruction of air passages and with atrophy of nerves or muscles and deformities of joints. If hemorrhagic diathesis is a complication of another disease, the physical signs of the primary disease may be manifest, such as those of infection, anemia, leukemia, lymphoma or cancer.

BASIC EXAMINATION OF BLOOD, URINE AND STOOL

In the basic examination of the blood, it may be possible at the time of capillary puncture and venipuncture to detect a prolonged bleeding time or an increase in capillary fragility. Anemia may or may not be present. The stained film of blood may permit the immediate detection of thrombocytopenia, leukemia, myeloid leukocytosis or other abnormalities that may serve as diagnostic aids. There may be hematuria or blood in the stool. There may be jaundice with choloria, acholic stools or variable evidence of disease of the liver.

MEASUREMENT OF CAPILLARY FRAGILITY

Principle

With rupture of capillaries the extravasation of blood into the skin forms a purple or purpuric spot. If there is a larger area of bleeding into the skin an ecchymotic area is formed that is dark red or blue, later changing to greenish or brown as the hemoglobin is converted, apparently, to biliverdin and bilirubin and subsequently removed.

Two terms are used to describe the susceptibility of capillaries to rupture and have resulted in some confusion. Both expressions have the same meaning, and thus it is correct to speak synonymously of *increased capillary fragility* or *decreased capillary resistance*. The ability of the capillary to withstand pressure is measured in two ways: by increase in the venous pressure by means of a blood-pressure cuff used as a tourniquet (tourniquet test), and by application of a known negative pressure to an area of the skin by the *Dalldorf*⁶⁵ method.

In the *Dalldorf method* a negative pressure equivalent to 200 mm of mercury is maintained for 1

TABLE 1 (Continued)

DISEASE	COMMENTS ON MECHANISM	BLEEDING TIME	COAGULATION TIME	CLOT RETRACTION	PLATELET COUNT	TOURNIQUET TEST	PROTHROMBIN CONCENTRATION	PROTHROMBIN CONSUMPTION
Hemophilia Deficiency in blood plasma of material required for normal coagulation	Bleeding results from deficiency of plasma factor probably thromboplastic in action. Hemophilia is sex-linked recessive hereditary disease occurring only in males and transmitted only by females. It is characterized by prolonged clotting time and marked susceptibility to hemorrhagic manifestations throughout life. Hemorrhages occur from trauma and appear 'spontaneously' affecting any tissue or organ. Hemarthroses are frequent. Administration of fresh whole blood, plasma or plasma fractions results in transient reduction of coagulation time toward normal with or without decrease in bleeding.	Initially normal, but puncture wound may subsequently bleed indefinitely	Prolonged in variable degree	Normal	Normal	Normal	Normal	Poor
Deficiency of fibrinogen fibrinogenopenia afibrinogenemia Deficiency or absence of fibrinogen	Abnormal bleeding is result of impaired blood coagulation. Deficiency or absence of plasma fibrinogen occurs rarely and may be associated with hemorrhagic symptoms and signs similar to those occurring in hemophilia but without hemarthroses. Absence of fibrinogen occurs as rare congenital anomaly. Acquired fibrinogenopenia may be complication of severe parenchymal disease of liver, or presence of plasma fibrinolysin.	Normal	Prolonged†	May be reduced	Normal	Normal	Normal‡	Normal
Parahemophilia (Owren's disease) Deficiency of Factor V of Owren	Disease has been reported only in females but males should be equally affected. It is probably hereditary and is characterized clinically, by epistaxis, ecchymoses following trauma, hematuria, menorrhagia and metrorrhagia. Hemarthrosis did not occur in Owren's patient. Congenital absence of factor in plasma required for conversion of prothrombin to thrombin results in prolongation of coagulation time and hemorrhagic manifestations. Addition of normal whole blood in vitro and in vivo corrects all laboratory and clinical abnormalities.	Normal	Characteristically prolonged	Normal	Normal	Normal	Normal§	Poor

†Coagulation of blood may be absent in afibrinogenemia. It may be quite normal until fibrinogen level is greatly reduced (levels of 50 to 75 mg per 100 cc).

‡Prothrombin concentration is normal but cannot be determined by one stage method since fibrinogen may be absent and must be added.

§Prothrombin time is prolonged by use of one stage Quick method but is normal if plasma-dilution technic is employed.

coagulation, determination of prothrombin activity and prothrombin consumption, all of which are described in detail below, and determination of fibrinolysins, determination of fibrinogen, vitamin C level of buffy coat, therapeutic trial with vitamin C and vitamin K and specific tests for circulating anticoagulants, which are discussed elsewhere.^{1, 6, 7-16}

It is frequently desirable or necessary to conduct other special examinations in patients with hemorrhagic diathesis to establish the diagnosis or response to treatment of the underlying disease process.

Special Tests for Hemorrhagic Disease

A partial list of special examinations that may be indicated in patients with hemorrhagic disease includes examinations of blood for leukemia, per-

nicious anemia and aplastic anemia, smear and biopsy* of bone marrow for morphology and number of platelets, and megakaryocytes, signs of neoplasia, aplasia and hyperplasia, biopsy* of lymph nodes or other structures, splenectomy as a therapeutic test in idiopathic thrombocytopenia or certain cases of secondary thrombocytopenia, examinations for the presence of infections, examinations of urine for drugs (sulfonamides, barbiturates and arsenic), x-ray examination of the gastrointestinal tract for bleeding, and study of the function of the liver as related to hypoprothrombinemia.

*All surgical procedures in a patient with hemorrhagic diathesis are done after consideration of possible complications of bleeding. In hemophilia, for example, surgical intervention may be hazardous even under carefully controlled conditions.

BLEEDING TIME

Principle

The bleeding time is the period required for effective hemostasis to occur after infliction of a standardized wound of the capillary bed. Bleeding time depends primarily on extravascular and vascular factors and to a lesser degree on factors of clot formation. It is an arbitrary biologic procedure with many limitations. Two methods are used at present: the Duke⁷⁰ method and the Ivy⁷¹ method. The former is employed most frequently.

Methods

Duke method A stab wound 2 mm in length and depth is made in the dependent portion of the lobe of the ear, a sharp-pointed scalpel blade, such as a Bard-Parker blade No 11, being used. The ear is not manipulated but must be warm. At intervals of half a minute, the blood accumulated on the skin is removed by gentle touching of the drop, but *not the skin*, with a blotter or piece of filter paper. The end point of this test is failure of blood to appear on the blotting paper when the drop is touched. The normal range for this method is from two to four and a half minutes. A needle should *not* be used for the capillary puncture, since the round hole does not bleed well enough to produce a sensitive test.

Ivy method A pressure equivalent to 40 mm of mercury is maintained on the arm with the use of a blood-pressure cuff. A puncture wound 2 mm in length and depth is made in a relatively avascular area of the forearm, just distal to the antecubital fossa. The escaping blood is absorbed on gauze pledgets and the bleeding time recorded to the nearest half minute. The normal range by this method has been reported⁶⁹ as 0 to six and four-tenths minutes, with a mean of three and two-tenths minutes.

Limitations and Interpretations

The difficulty of producing a standardized wound considerably limits this test as an aid in diagnosis. This limitation occurs also with the use of a mechanical lancet. Slight increases in bleeding time above the upper limit of normal always require that a series of such tests be made to control the variation in producing the wound and to determine the state of hemostasis. Under no circumstances should a needle be used for the puncture, since a significant increase in bleeding time may be missed that is readily demonstrable by a stab wound made by a scalpel blade.

An increase in the bleeding time does not permit a specific diagnosis to be made, nor does it signify an abnormality of a single mechanism. Prolongation of the bleeding time may be encountered in conditions in which the efficiency of the *extravascular factors of hemostasis* is decreased. Thus,

in *aged persons*, prolongation of the bleeding time due to poor tissue tone and atrophy of subcutaneous tissue may be encountered. As a result of these senile changes, the hydrostatic pressure in the surrounding tissue may not rise to effective levels when bleeding from the vessel occurs. In addition, flabby and sparse subcutaneous tissue is not conducive to proper mechanical plugging of the open end of the vessel as it retracts.

Abnormalities in the bleeding time may also result from changes in the *vascular factors of hemostasis*. Thus, in states in which there is altered capillary contraction the bleeding time may be prolonged. In senility, poor vascular contraction may be a factor, in conjunction with poor tissue tone and tissue atrophy, to account for the sporadic prolonged bleeding time that is observed. In "*thrombasthenia*" there may be extremely variable increases in the bleeding time, which are considered to be due to altered capillary contraction since the number of platelets is normal.^{2, 20-23, 25-27} A dogmatic conclusion that altered capillary contraction is the sole mechanism for prolongation of the bleeding time in this disease cannot be made since the platelet is of considerable importance in controlling the duration of the bleeding time. There is evidence that the platelets in "*thrombasthenia*" may not agglutinate normally,⁷² and it is possible that they do not form a stable plug in the open end of the vessel to aid in effective hemostasis.

Abnormalities in *factors of clot formation*, such as failure of formation of the platelet plug in thrombocytopenia, may be a contributing cause of a prolonged bleeding time.^{4, 5} Conversely, frank alterations in blood coagulation have little effect on the duration of the bleeding time. In *hemophilia* the bleeding time, as arbitrarily defined here, is "normal" in that bleeding stops within three minutes. This is explained on the basis that in hemophilia the initial vascular contraction is normal, and this, in conjunction with small amounts of tissue juice for partial coagulation, temporarily causes cessation of bleeding.² At a later time, such as an hour after the test, when vascular contraction has ceased, the stab wound may begin to "ooze" and bleed slowly and continuously, apparently owing to poor clot formation. The bleeding may continue until the wound is treated with thromboplastic material. Similarly, in *afibrinogenemia* the bleeding time is "normal" as a result of adequate initial vascular contraction and proper functioning of the extravascular factors concerned in hemostasis. As in hemophilia, oozing may occur later and continue unabated until fibrinogen is administered. A test of bleeding time in a known hemophilic patient or one with afibrinogenemia is to be *avoided* as an unnecessary *surgical* procedure. On the contrary, venipuncture with a 20-gauge needle is done whenever indicated and should *not* cause bleeding if

minute over a circular area 1 cm in diameter on the outer side of the upper arm, and the number of petechiae produced are counted. Fewer than 10 petechiae were observed by Aggeler, Howard and Lucia⁶⁹ in 92 per cent of 64 normal subjects tested, with a range of none to more than 30. Although the Daldorf method has certain advantages, such as reproducibility and ease of quantitative measurement, it requires specialized apparatus that is not usually available. The tourniquet test or positive-pressure method is most commonly used and is described below.

Tourniquet Test for Capillary Fragility

The forearm and hand are inspected in advance of the test for purpuric spots, nevi and hemangiomas that might be confused with petechiae produced by the test. These are marked with a ring of ink. A blood-pressure cuff is applied about the upper arm in the usual manner, and the *blood pressure accurately determined*. Although the usual procedure employs a pressure midway between systolic and diastolic pressure for five minutes, it is *recommended* that a pressure equivalent to 100 mm of mercury be employed for *ten minutes*. (If the patient's systolic blood pressure is 100 or less, a pressure is used that is midway between systolic and diastolic pressure.) After ten minutes the cuff is removed, and five minutes later the forearm, hand and fingers are examined on all sides for petechiae. One may devise a refinement by drawing a circle 5 cm in diameter, located on the flexor surface of the forearm, 2.5 cm below the antecubital fossa. The petechiae in this area are counted. It is recommended that a normal subject be examined as a control and as an aid in estimating the degree of abnormality of a positive test.

Limitations and interpretations. Normal subjects show no petechiae or a few scattered petechiae just below the margin of the cuff. In a circle 5 cm in diameter, the upper limit of normal is approximately 10 to 15 purpuric spots (adequate data for the range of normal are not available). In positive tests, the entire forearm and hand may show myriads of petechiae that may be separate or confluent.

The result on the whole arm is *graded* in a crude manner from + to ++++ as follows: +, slight increase over normal; ++, many petechiae over the anterior surface of forearm; +++, multiple petechiae over the whole arm and dorsum of the hand; and ++++ confluent petechiae in all areas of the arm and dorsum of the hand. *It is emphasized that a significant increase in capillary fragility may be missed by the use of a pressure below 100 mm of mercury for only five minutes or a pressure equivalent to 100 mm of mercury when the systolic blood pressure is less than 100.*

The tourniquet test is primarily a measurement of the integrity of the *vascular factors* in hemo-

stasis. The degree of positivity, however, is also a measure of the extravascular factors as well as the factors of clot formation, since blood must leave the vessel if a petechia is to be formed. Once blood escapes from the vessel lumen, factors in the surrounding tissue and within the blood itself come into play. Although an increase in capillary fragility does not permit a specific diagnosis to be made, certain facts are known.

In *scurvy*, there may be marked hemorrhagic diathesis characterized by an extreme increase in capillary fragility with formations of hematomas, apparently related to deficiency of intercellular collagen substance. There is no abnormality of the other special tests, as shown in Table 1. It is particularly noteworthy that the bleeding time is normal in scurvy and that the abnormal capillary fragility disappears in a few days after administration of vitamin C or orange juice.

In "*thrombasthenia*," a disease or group of diseases² of unknown origin, the capillaries have been reported to be abnormal in shape and in contractility; there is usually an increase in capillary fragility, but the number of platelets is normal.² The capillary fragility may be normal or abnormal (Table 1).

In severe *thrombocytopenia* of primary or secondary origin there usually occur bleeding from mucous membranes, purpura, increased capillary fragility, prolonged bleeding time and decreased clot retraction. There is considerable evidence from Macfarlane,² Bedson²⁹ and others that the abnormality of the capillary may result from poor contraction of the capillary, but the relation to thrombocytes is not defined. There is also evidence that the site of petechial hemorrhage is the arterial end of the capillary loop.⁶⁸ Although normally the platelets aid in "plugging" breaks in the capillary, it has been shown that there is a failure of this "plugging" in thrombocytopenic states^{4, 8} and that vasoconstriction of the severed and the adjacent vessels does occur. These observations do not agree with those of Macfarlane.² Although purpura and bleeding from mucous membranes occur in most cases of *severe thrombocytopenia*, there are well established exceptions. For example, after splenectomy there may be a prompt return to normal of the capillary fragility and bleeding time before there is a rise in platelets or during continued thrombocytopenia. In addition, there may be thrombocytopenia with normal capillary resistance and normal bleeding time.

In *allergic purpura* the tourniquet test may be extremely variable, presumably owing to abnormalities of the capillaries but of unknown mechanism. The same reservation is true of the purpura of sepsis.

to be normal or average in polycythemia. A case of hyperglobulinemia has been observed in which the fluid volume was greatly increased even though the level of platelets and amount of fibrinogen were normal.⁷² Thus, clot retraction may be affected not only by platelets but also by decreased fibrinogen, by the number of red blood cells and by elevated plasma proteins.

For the *qualitative method*, clot retraction occurs normally in an hour, forming a small, firm red elastic mass. In abnormal conditions clot retraction may not occur at all in twenty-four hours, or there may be variable degrees of retraction.

Classically in *thrombocytopenia*, with a platelet count below $100 \times 10^3/\text{mm}^3$, there is decreased clot retraction that is roughly proportional to the platelet count. In the semiquantitative method there may be no clot retraction, so that 100 per cent of the fluid volume is retained in the clot (no serum is expressed).

In "*thrombasthenia*" the platelet count is usually normal, but the clot retraction is frequently poor, suggesting abnormal function of the platelets.

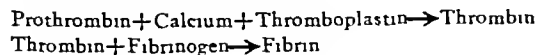
In certain cases, as in medical and surgical shock, a so-called fibrinolysin,⁷³ which may obscure clot retraction by actual dissolution of the clot, develops.

Clot retraction is normal in the remaining hemorrhagic diseases (Table 1).

MEASUREMENT OF COAGULATION TIME OF VENOUS BLOOD IN GLASS TUBES — CLOTTING TIME

Theory of Blood Coagulation

Many of the factors concerned in clot formation are as yet poorly understood. Until recently the following fundamental equations of blood coagulation had remained unchanged:



This relatively simple schema was proposed by Morawitz¹⁸ in 1905, and it is recommended that it be used as a framework into which new factors can be fitted.

"*Prothrombin accelerators*" of plasma and serum. Almost simultaneously, from four different laboratories, there have recently appeared descriptions of a substance in plasma that is concerned with the speed of formation of thrombin from prothrombin. In Norway, Owren¹⁹ has designated the substance "Factor V", in Australia it was called "accelerator substance",²⁴ one group in the United States has designated it "plasma accelerator globulin",²⁵ another has called it "labile factor".²⁶ These various terms have led to confusion, and it is still uncertain whether they are designations of the same substance, for clarity in writing, however, they may be grouped into a single term,

"prothrombin accelerators" of plasma. In addition to these "prothrombin accelerators" of plasma, three "prothrombin accelerators" of serum have been described. Owren¹⁹ uses the term Factor VI, Ware and Seegers⁶¹ speak of serum accelerator globulin, and Alexander⁶⁴ terms his substance serum prothrombin conversion accelerator (SPCA). Again, it may be that these three terms designate the same substance, although conclusive evidence of this is lacking. Also, it is likely that the "prothrombin accelerators" of serum are derived from the "prothrombin accelerators" of plasma, much as thrombin of serum is elaborated from prothrombin of plasma. The serum "prothrombin accelerators" are considered to be the active substances accelerating the conversion of prothrombin into thrombin, whereas the plasma "prothrombin accelerators" are relatively inert.⁶¹

There is little doubt that these "prothrombin accelerators" exist, since deficiencies of these components have been described as parahemophilia by Owren²² and plasma accelerator globulin deficiency by Seegers and Craddock.⁵⁹ Although a clinical deficiency of labile factor has not been described as such, Quick and Stefanini⁶⁶ have suggested that the case described by Rhoads and Fitz-Hugh⁵⁷ probably represented such a deficiency.

Platelets in conversion of prothrombin to thrombin. It has been shown by Quick⁶⁵ and confirmed⁶⁰ that platelets are concerned with the total conversion of prothrombin to thrombin, and to a lesser degree with the speed of this reaction.⁶⁰ It has been demonstrated that the thromboplastin in platelets is not responsible for this activity,⁶⁰⁻⁶⁵ which has been described by Quick as "platelet enzyme" or thromboplastinogenase. It is Quick's concept that platelets are necessary for the activation (by an enzyme) of thromboplastinogen to thromboplastin, which in turn, in the presence of calcium, will convert (stoichiometrically) prothrombin to thrombin.⁶⁰

Hypothesis of blood coagulation. To build these new factors into the framework of Morawitz is as yet a theoretical and controversial problem. By a combination of the theories of blood coagulation of Quick⁶⁶ and Ware et al.⁶⁰ it is possible to make a *working hypothesis* for the location of all components.

It has been shown⁶¹ that the plasma "prothrombin accelerators" have essentially no effect on the yield of thrombin produced from a mixture of *purified* prothrombin, thromboplastin and calcium. It is established that the *serum* "prothrombin accelerators" cause a large evolution of thrombin in such a mixture.¹⁹⁻⁶⁰⁻⁶⁴ Therefore, it becomes necessary to show graphically the conversion of the "prothrombin accelerators" of plasma to those of the serum type. Although the mechanism for such conversion has not been clearly shown, it may be

gentle pressure is maintained over the site for five to fifteen minutes after the puncture

The bleeding time is normal in hemorrhagic states in which the only abnormality is increased capillary fragility. Thus, the bleeding time in *scurvy*, *allergic purpura* and *sepsis* is normal even though the tourniquet test is positive

PLATELET COUNT

The finding of thrombocytopenia does not permit an etiologic diagnosis to be made. The diagnosis of so-called idiopathic thrombocytopenia (purpura hemorrhagica) is made largely by the exclusion of conditions known to produce secondary thrombocytopenia. The role of thrombocytopenia in hemorrhagic diathesis can only be defined, in part, as pointed out above. Thrombocytopenia does not usually produce a prolongation of coagulation time as measured by the usual technic in glass, but definite prolongation of coagulation is easily demonstrable in glassware coated with silicone (Dri-film)⁷³

The blood platelet has also been shown to be an important factor in blood coagulation as indicated by its effect on the conversion of prothrombin to thrombin,*⁶⁶ since the lower the platelet count, the poorer this conversion. In addition to the disturbed coagulation (in silicone-coated glass) in thrombocytopenia, there is always associated *poor clot retraction*⁶⁶. The defects in coagulation (poor clot retraction, and decrease in adhesiveness, in rigidity and in contractility) may be factors, associated with the failure to form platelet plugs, that explain in part the bleeding tendency in thrombocytopenia

CLOT RETRACTION

Principle

Venous blood, containing all the factors necessary for coagulation and possessing no coagulation inhibitors, will clot spontaneously when placed in glass tubes. The clot when formed is usually a homogeneous suspension of red cells in plasma. Occasionally, if the red cells sediment rapidly or if coagulation is greatly prolonged, the clot will have an upper layer containing fibrin but no red cells and a lower layer of red clot. In either event, when the clot stands the fibrin contracts, expressing serum from the clot. This process is described as clot retraction or syneresis. In general, the correlation between poor clot retraction and thrombocytopenia is so close that an observed decrease in clot retraction may be a more reliable index of thrombocytopenia than the platelet count itself. As a corollary, a normal degree of clot retraction is good evidence that the platelet count is approximately $100 \times 10^3/\text{mm}^3$ or more. The relation of

platelet function to clot retraction is not well understood

Methods

Qualitative methods Clot retraction can be measured qualitatively by inspection as follows. 2 cc of blood is obtained by venipuncture during the coagulation test, as described below. The tube is placed in a water bath at 37.5°C and observed after half an hour and one, two, four and twenty-four hours for signs of retraction—namely, the separation of the clot with expression of serum. The clot may stick to the wall of the tube and require gentle separation if retraction has not occurred within an hour. This is done by gentle rimming of the top of the clot with a platinum wire or wooden applicator.

Semiquantitative method *Fluid volume of the clot* A semiquantitative method has been described by Macfarlane⁷⁴ and modified slightly by Aggeler, Lucia and Hamlin⁷⁵ and others^{76, 77}. In this method 5 cc of venous blood is introduced into a 15-cc graduated centrifuge tube. A cork fitted with a copper wire bent in the form of a hook is adjusted so that the hook is immersed in the upper layers of the blood. The tube is placed in a water bath at 37.5°C, and the coagulation time noted. One hour after coagulation the total volume (T) of the specimen is recorded and the retracted clot is removed by means of the hook. The residual volume of serum (S) is recorded, and the volume occupied by the clot (C) is taken to be $T - S$. The hematocrit is determined, in the usual manner on another portion of the blood sample, and the total corpuscular volume percentage (PCV) of formed elements is read, including the layers of white cells and of platelets. To calculate the fluid volume FV *occluded within the clot*, in percentage, the following expression is used: $\text{FV (percentage)} = [(C/T) \times 100] - \text{PCV}$. The normal range is reported as 6 to 20 per cent,⁶⁹ with a mean of 8 per cent.

Limitations and Interpretations

It is known that platelets are directly concerned with clot retraction so that good clot retraction is usually associated with normal platelet counts. However, there are various degrees of clot retraction as evidenced by moderate retraction of the clot with platelet counts of 35,000 to 40,000.⁶⁶ Other factors may influence the appearance of the clot in retraction. A reduction in fibrinogen results in the formation of a small clot that gives the false impression of normal clot retraction. Similarly, a reduction of erythrocytes, as in anemia, gives a false impression of normal clot retraction. Conversely, in polycythemia there appears to be poor clot retraction as shown by the qualitative method since the clot is large and the serum small in volume. By the use of the semiquantitative method, the volume percentage of entrapped serum is found

*Prothrombin consumption

introduction of tissue fluid from a traumatic venipuncture, agitation of the blood by rapid passage through the needle, introduction of air bubbles or traumatic transfer of blood to the test tubes and unclean or rough glassware. Prolongation of the coagulation time may occur as a result of the following variations in technic: unduly low or high pH, unduly low or high temperatures and the use of plastic tubes or tubes coated with paraffin or nonwetable plastics (silicone-Dri-film). In view of these facts it is quite important to carry out the test at controlled temperature, pH, and calcium concentration and with techniques that avoid trauma in the venipuncture, the introduction of air bubbles and unduly rough treatment of the blood obtained. The time for coagulation to occur is a purely relative test and does not indicate that complete coagulation has occurred for the whole column of blood. It is simply a measure of the time required for the formation of fibrin at the air interface in quantity sufficient to support the column of blood when the tube is inverted.

The coagulation time of whole blood is prolonged notably in *hemophilia* and after administration of *heparin*, varying from fifteen minutes to several hours. In general, the degree of elevation of the coagulation time is a function of the severity of the disease in hemophilia and of the effect of heparinemia. On the other hand, it has been noted that hemophilic patients with greatly prolonged coagulation times may have fewer hemorrhagic episodes than others with only slight prolongation of the coagulation time. The coagulation time of blood of a given hemophilic patient remains remarkably constant except when altered therapeutically.

In severe cases of *hypoprothrombinemia*, the coagulation time is also prolonged, but this test is unreliable as an index of prothrombin deficiency, since an increase in coagulation time is a late manifestation and indicates an extremely low and dangerous level of prothrombin, 5 per cent or less.⁴⁴ Only small amounts of prothrombin are necessary for the formation of thrombin and the subsequent fibrin formation that results in visible coagulation of blood. Accordingly, the coagulation time cannot be used with safety in following the course of hypoprothrombinemia resulting from Dicumarol therapy.

Prolongation of coagulation time is observed in *fibrinogenopenia* and completely incoagulable blood is encountered in absolute *afibrinogenemia*, whether congenital or acquired. The latter may be due to large amounts of fibrinolytic, as in shock.

Prolonged coagulation time is also encountered in *parahemophilia*⁵³ (Owren's disease), being due, in this instance, to a deficiency of the so-called "Factor V" of Owren.

The finding of prolongation of the clotting time is nonspecific information since it does not of itself indicate the presence of hemophilia, the absence

of fibrinogen, a deficiency of a "prothrombin accelerator" or the effect of heparinemia. As mentioned above, the coagulation time in hemophilia may be restored toward normal after treatment at a time when the patient is showing active hemorrhage.

If the test is carried out in glass tubes, a decrease in coagulation time below six minutes has no reliable clinical value as a measure of increased coagulability of blood, such as may occur in certain diseases with abnormal tendency to thrombosis. Strictly, the coagulation time should be used only in relation to plasma coagulation defects and coagulation inhibitors such as heparin.

(To be concluded)

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as suggested by Ware and Seegers,⁶¹ that thrombin plays a part in this reaction as follows

Prothrombin + Thromboplastin + Calcium → Thrombin
 Thrombin (?) + Plasma "prothrombin accelerators" →
 Serum "prothrombin accelerators"
 Prothrombin + Serum "prothrombin accelerators" → Thrombin
 Thrombin + Fibrinogen → Fibrin

Since Quick⁶⁶ has shown *platelets* to be important in this reaction, it is possible to eliminate the one weak point of the foregoing theory — namely, that purified prothrombin, tissue thromboplastin and calcium form little or no thrombin.^{19 61} With the "platelet enzyme" activating plasma thromboplastinogen, there results augmentation of thrombin formation as follows

"Platelet enzyme" + Thromboplastinogen → Thromboplastin
 Prothrombin + Thromboplastin + Calcium → Thrombin

The next step then involves conversion of the plasma "prothrombin accelerators" to the active serum "prothrombin accelerators" by thrombin. Thus, the theoretical steps in the coagulation of blood can be combined into a *working hypothesis*, involving the following five steps

"Platelet enzyme" + Thromboplastinogen → Thromboplastin
 Thromboplastin + Prothrombin + Calcium → Thrombin
 Plasma "prothrombin accelerators" + Thrombin (?) →
 Serum "prothrombin accelerators"
 Prothrombin + Serum "prothrombin accelerators" → Thrombin
 Thrombin + Fibrinogen → Fibrin

With this concept one can endeavor to interpret abnormalities in the various laboratory tests that utilize the coagulation of blood or plasma as an end point

Coagulation Time of Venous Blood

Principle When unaltered venous blood, obtained by a nontraumatic venipuncture, is introduced into glass tubes the time required for clotting to occur is called the coagulation time or clotting time. This is a highly arbitrary biologic procedure since the glass surface and many other factors affect the coagulation time significantly. For example, normal blood collected in tubes made of a plastic, or tubes coated with paraffin or nonwetting agents such as silicone, requires a significantly longer time to clot (thirty to sixty minutes) than in glass tubes (six to twelve minutes). The temperature of shed blood profoundly affects the clotting time, as evidenced by the extreme prolongation (one to four hours) at a temperature of 3°C

as opposed to the relatively rapid clotting (six to twelve minutes) occurring at body temperature. Technically, the modified⁸ Lee-White method for measurement of blood coagulation time is probably as reliable a procedure as is available currently. It should be remembered, however, that coagulation times obtained by this method are purely relative, and that the method is of value primarily as a screening procedure in an effort to determine plasma coagulation defects and anticoagulant activity. *The method of measurement of the coagulation time by the use of capillary blood drawn into a capillary tube is so unreliable as to be valueless, it should not be used*

Method (modified Lee-White method) A sterile 5-cc syringe and sterile needle are rinsed twice with sterile physiologic saline solution, and all the solution is expelled. A venipuncture is performed with the least possible stasis and trauma. The tourniquet is applied just before the venipuncture is made. Traction on the plunger of the syringe — if used at all — should be gentle, to prevent agitation of the blood and to avoid the entry of air bubbles into the syringe as the sample is drawn. If the vein is not entered on the first attempt, the needle and syringe should be discarded,* and another sterile syringe and needle, rinsed twice with sterile saline solution, employed. A sample of 5 cc of blood is obtained, the needle is removed from the syringe, and 2-cc samples of blood are placed in each of two chemically clean test tubes (13 by 100 mm) that have been previously rinsed twice with physiologic saline solution. The blood should be made to run down the side of the tube *gently* to avoid agitation. The remaining 1 cc of blood in the syringe is discarded since it contains unavoidable traces of tissue juices.* The two tubes are placed in a water bath at 37.5°C, and at intervals of approximately a minute one of the tubes is observed for clotting by removal from the bath and gentle tilting. The end point of coagulation is reached when the tube can be inverted without loss of contents. When this occurs for the first tube, the second is observed in a similar manner, until coagulation occurs in it. The beginning of the test is the time when blood first enters the syringe. The average time, in minutes, required for blood to clot in the two tubes is reported as the coagulation or clotting time. If there is a difference of more than five minutes between the coagulation times of the two tubes, the longer time is reported. This is commonly found in hemophilia.

Limitations and interpretations The normal range (100 subjects) is from four to twelve minutes, with a mean of seven and seven-tenths minutes and a standard deviation of one and seven-tenths minutes.³⁹ Most errors in technic will tend to *shorten* the coagulation time, such errors include

*The tissue juices contaminating the needle and syringe from an unsuccessful venipuncture will decrease the coagulation time

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 35441

PRESENTATION OF CASE

A seventy-two-year-old Finnish-born married steel worker entered the hospital with a chief complaint of "severe" shortness of breath.

Two years before entry the patient was told that he had an "irregular" heart but successfully discharged his duties as a steel worker until eleven months before entry, when he tripped and fell 20 feet while on the job and injured the left seventh, eighth and ninth ribs anteriorly and his left hand. Radiograms of the chest were reported as not remarkable except for the rib fractures. After spending twelve days in two other hospitals he returned home but not to his job. The patient dated the beginning of his dyspnea as shortly after this accident. About nine months before admission vague precordial pain, described by the patient as "constriction" and "congestion," appeared especially after exertion but frequently at night. This discomfort lasted usually about five minutes but occasionally much longer and did not always disappear with rest. No radiation of pain to the shoulders or arms was ever present. The dyspnea temporarily improved three and a half months before entry so that he was content to take care of his flock of turkeys and do other small jobs. However, his dyspnea recurred in the next month, and he was denied even these minor pleasures, being unable to walk short distances without excessive fatigue. A slight cough productive of small amounts of whitish sputum appeared. About five weeks before entry he developed hay fever (which he had experienced in the past) and noted more difficulty sleeping at night, requiring two pillows to sleep comfortably. One month before entry he noted an increase in his anorexia, which he believed had been present since his accident. He further noted a weight loss of about 20 pounds in the last five or six months.

He visited the Medical Clinic of the Out Patient Department one month before admission, and an additional history was obtained of exposure to tuberculosis, a daughter had the disease several years previously and a sister-in-law was similarly afflicted thirty years before. Examination at this time revealed a blood pressure of 150 systolic, 90 diastolic, a pulse rate of 80, with 8 to 10 skipped beats at the wrist per minute, and a Grade II apical systolic murmur and auricular fibrillation, no definite cardiac enlargement was noted. The temperature was 97°F, and the respiratory rate 20. The lungs were resonant, and basilar rales cleared on coughing. A firm,



FIGURE 1

nontender right supraclavicular node (1.5 cm in diameter) was noted. Abdominal and rectal examinations were not remarkable. A blood Hinton test was negative. Urinalysis was negative. Radiograms of the chest revealed an enlarged heart (Fig 1) with a cardiothoracic ratio of 18/25, the enlargement appearing predominantly in the region of the left ventricle. The lung fields exhibited extensive, diffuse, linear and mottled densities, particularly in the middle and lower portions. The hilar vascular shadows were poorly seen but appeared somewhat enlarged. The patient was digitalized and given nitroglycerin.

Two weeks before entry he was again seen in the Medical Clinic, at which time his blood pressure was 130 systolic, 80 diastolic, and the pulse and breath

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DR BRAILEY Could the shadows in the lung be tuberculosis?

DR McCORT There is no evidence of cavitation or calcification to indicate tuberculosis

DR BRAILEY Do you think the shadows are due to embolization?

DR McCORT Multiple small emboli could produce similar nodular densities, but there are strand-like densities in addition to nodules

DR BRAILEY Have you ever seen metastatic carcinoma present this kind of picture?

DR McCORT A small percentage of metastatic carcinomas show a lymphatic permeation that is compatible with this picture

DR BRAILEY There is no interference with the bronchi as far as you can see—no obstruction?

DR McCORT There is no narrowing or obstruction of the bronchi

DR BRAILEY This man was said to have an "irregular" heart for two years. We may assume that it was fibrillating for at least that long. The heart was really enlarged, he had a Grade II systolic murmur, and an abnormal electrocardiogram. The tracing was not inconsistent with infarction, nor was it inconsistent with left ventricular strain and digitalis effect. Would you agree with that, Dr Bland?

DR BLAND It sounds like an aging heart to me—a nonspecific electrocardiogram, showing the effect of digitalis, I would think.

DR BRAILEY What was the nature of the defect? Did he have rheumatic heart disease? Somewhat in favor of that diagnosis is the long-standing fibrillation. But patients with rheumatic heart disease rarely live to seventy-two years of age and no diastolic rumble was ever described. It does not seem reasonable to consider rheumatic heart disease here.

Did he have hypertensive and arteriosclerotic heart disease? The blood pressure was repeatedly reported as normal. If he had had hypertension in the past of sufficient degree and duration to result in a heart of this size, surely he would have been in severe congestive failure when the blood pressure fell to this level. But the evidence for congestive failure is not very impressive, even two weeks before he came into the hospital. He had marked dyspnea, to be sure, about which we will say more later, but he had no peripheral edema. The liver was not thought to be enlarged, and only transient rales were heard in the chest.

What else might reduce his hypertension other than heart failure? A failure of the adrenal cortex might do so. To be sure, little was said of fatigability, and there were no pigmentary changes recorded. But we wonder a bit about the adrenal glands because we are tantalized by the information that he was exposed to tuberculosis and the serum sodium was remarkably low, perhaps because he was on a low-sodium diet. He had not had it long, however.

Perhaps coronary-artery disease without a large infarct but with widespread microscopic scarring of the myocardium, was a factor here. The electrocardiogram would not be inconsistent with this possibility. He is said to have had ill described pain, which may have been angina and was probably considered as such since he was given nitroglycerin.

The dyspnea troubled him greatly and certainly troubles me. There are many causes for dyspnea, but if we confine ourselves to those that occur in the chest, they can be roughly divided into pulmonary and cardiovascular. Of the vascular causes, disease on the arterial side of the pulmonary circuit should have resulted in cor pulmonale. He had a tremendous heart, and the right ventricle and right auricle were enlarged. I am not at all sure that he did not have cor pulmonale. He had little evidence of peripheral right-sided heart failure until the last few days of life. Trouble on the venous side of the pulmonary circuit should have resulted in pulmonary edema, of which we have little or no evidence. We are struck by the curious lack of parallelism between his increasing dyspnea and his apparent cardiac performance as reported. It seems certain that he did not have enough cardiac failure per se to account for a vital capacity of 900 cc and that he must have had some pulmonary disease as well. He undoubtedly had some senile emphysema, but I think this picture presented by his x-ray films is very curious and I suspect that he had something else—either embolization with marked widespread fine scarring of the lungs, or an endarteritis.

The evidence for cancer consists of hard nodules, which may have been metastatic supraclavicular lymph nodes, and two gastric washings containing tumor cells. Where shall we put this malignant lesion, which must have been either exfoliating or ulcerating? Is it fair to ask if these cells were epithelial in type?

DR TRACY B MALLORY They were interpreted as that.

DR BRAILEY The obvious answer is carcinoma of the stomach, but if we plump for carcinoma of the stomach, we have to make the diagnosis in the face of normal gastric acidity, a not impossible situation but nevertheless rare. The sputum contained no tumor cells on one examination. That does not exclude tumor of the lung. The patient had a productive cough, and it was noted that he swallowed most of his sputum. I do not see why he might not have swallowed the cells for that matter although we do not usually look for carcinoma of the bronchus by doing gastric washings. Metastatic pituitary glands in the neck occur secondary to carcinoma of the stomach, but they are even more commonly found secondary to bronchial disease. It is possible that we shall find no explanation for the low serum sodium. It was probably the result of the low-sodium diet or the edema. But if he did have damage in the adrenal glands by any chance, it is possible that they were

sounds were essentially unchanged. Very shortly thereafter the dyspnea rapidly increased, three or four pillows being required at night. Five days preceding entry the dyspnea became so severe that virtually no sleep was obtainable, the patient having to sit in a chair or upright in bed to facilitate easy breathing. The next day he developed ankle edema, which gradually increased.

Physical examination on admission revealed a well developed, well nourished, somewhat apprehensive but co-operative man with extraordinary dyspnea, coughing frequently and usually swallowing the sputum. Cyanosis of the lips, fingers and mucous membranes was present. Bilateral distention of the neck veins, slightly more marked on the left, was evident in the upright position. A few small, hard nodes were present in each supraclavicular region. The chest was moderately emphysematous, and dullness was present on the right posteriorly and in the axilla to the angle of the scapula, with decreased breath and spoken voice sounds, dry rales were present in the right chest above the area of dullness, but no rales were noted on the left. The notable cardiac signs were a maximal impulse of the heart 11 cm. to the left of the midsternal line in the lower fifth interspace, auricular fibrillation with a 10-beat pulse deficit, some occasional bigeminy, and a short apical systolic murmur. Moderate ankle and slight to moderate sacral edema was present.

The temperature was 97°F, the pulse 80, and the respirations 32. The blood pressure was 135 systolic, 90 diastolic.

Investigative studies revealed a circulation time (Decholin) of 50 seconds, a venous pressure equivalent to 222 mm. of water and a vital capacity of 900 cc. Examination of the blood disclosed a red-cell count of 5,100,000, with a hemoglobin of 14.5 gm., and a white-cell count of 9550, with 80 per cent neutrophils. The prothrombin time was 19 seconds (normal, 15 seconds). The nonprotein nitrogen was 28 mg., the blood sugar 96 mg., and the total protein 5.9 gm. per 100 cc., and the sodium 127.8 milliequiv., the chloride 92 milliequiv. and the carbon dioxide 22.7 milliequiv. per liter, the alkaline phosphatase was 4.6 units per 100 cc. The phenol-sulfonephthalein test showed 62 per cent excretion of the dye, and the bromsulfalein test 64 per cent retention of the dye. The gastric acidity was in the normal range. Sputum smears were negative for acid-fast organisms and abnormal cells. Two separate gastric washings were positive for tumor cells and gave a ++++ guaiac reaction. The stools were consistently guaiac positive. Urinalysis was not remarkable, the urinary sodium chloride was 1 or 2 gm. per 24 hours. An electrocardiogram revealed auricular fibrillation, low voltage, sagging ST segments in Lead 1 and 2 and AVL and V₆, and inverted T waves in Lead 1 and 2 and AVL and V₆ and V₆.

Radiographic studies demonstrated very little change in the chest since the previous examination. A roentgenogram of the abdomen was marred by the dyspnea, the only discernible visceral outline being that of the liver, which was at the upper limits of normal, some air was present in the large bowel, and little or none in the small bowel. A gastrointestinal series was attempted but was incomplete and unsatisfactory because of the patient's extreme illness, however, the midportion of the posterior wall of the stomach appeared to be rather straight, and the duodenal bulb was deformed. X-ray films of the bones were normal.

The patient was placed on a cardiac regime, including digitoxin, ammonium chloride, Sodium Amytal, Mercuhydrin, a diet moderately low in sodium, and other supportive therapy. Despite these measures he continued to be critically ill and died on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR ALLEN G BRAILEY* It is hard to know what to take up first when one is confronted with this welter of signs and symptoms. We might begin by seeing the x-ray films.

DR JAMES J McCORT On the initial chest examination the strand-like and coarse and finely nodular increase in density in both lungs is well seen. These changes extend outward from the hilus to the periphery and involve the greater portion of both lungs. There is no fluid in either costophrenic sinus. The heart is markedly enlarged to the left and right (Fig 1), and there is definite fullness anteriorly, suggesting right ventricular enlargement. A widening of the hilar shadows is seen, suggesting dilatation of the main pulmonary arteries. A film of the chest made one month after the first examination shows very little change except possibly a small amount of fluid in the right costophrenic sinus.

Examination of the gastrointestinal tract was unsatisfactory because of the severe dyspnea. The esophagus was normal. On one film a flattening of the posterior wall of the stomach near the lesser curvature is demonstrated. There is also a slight constriction of the duodenal cap and a small diverticulum of the second portion of the duodenum.

DR EDWARD F BLAND Are the bones all right?

DR McCORT The skull and long bones were not abnormal.

DR BRAILEY What about the possibility of a pathologic fracture two years before admission?

DR McCORT I can see no evidence of it.

DR BRAILEY There is enlargement of the heart. Is it mostly right or left ventricle? The protocol says "left."

DR McCORT It is impossible to determine which ventricle is larger. There is definite right ventricular enlargement.

*Assistant physician, Massachusetts General Hospital.

chest, increasing on deep inspiration. The pain persisted for several weeks and then slowly subsided. There was no cough, sputum, hemoptysis, nausea, vomiting or weight loss. Three weeks before admission while in Canada on a vacation, she consulted a physician. After fluoroscopic examination she was told that she had pleurisy. She received pills for pain and returned home. Since then she was up and around doing housework. During the year before admission she noted a lump in the suprapubic region that swelled intermittently.

At the age of eighteen she had "wet pleurisy" on the right side and was treated at home by a homeopathic physician. Her father and mother were alive and well. Two of nine siblings had died of tuberculosis, but the patient had had no contact with them. An aunt and cousin had died of cancer.

Physical examination showed a well developed, well nourished woman who looked quite healthy. Her lungs were clear to percussion and auscultation. She took deep breaths without apparent difficulty. There was no pain over the ribs. The heart showed a normal sinus rhythm, and no murmurs were heard. Abdominal examination showed no spasm or tenderness. A large, irregular suprapubic mass was present. Pelvic examination confirmed this mass in the posterior cul-de-sac, which extended down to the posterior rim of the cervix. The cervix was not fixed but showed erosions about the external os.

The temperature, pulse and respirations were normal. The blood pressure was 128 systolic, 88 diastolic.

The white-cell count was 7800, and the hemoglobin 12.5 gm. The urine was normal. Cytologic examination of vaginal smears was negative. A chest x-ray film showed scars, a number of which were calcified, in the right upper lobe and to a lesser extent in the left upper lobe. The heart and aorta were not unusual. The nonprotein nitrogen was 19 mg, and the total protein 6.0 gm per 100 cc.

An operation was performed.

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DR CASTLEMAN Nothing is supposed to be withheld.

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The problem, it seems to me, and I may be wrong, but this is the way I looked at it is to try to correlate the large suprapubic mass, without any other

adjective attached, with the pain in the right chest. I think it is somewhat difficult. Dr Hanelin, can you help me?

DR JOSEPH HANELIN I doubt it very much.

DR HAMLIN You are my last hope.

DR HANELIN The chest film shows old areas of scarring in both upper lung fields. The left and right costophrenic sulci are clear. There is faint increased density at the right base, which may be due to old pleural thickening.

DR HAMLIN Is there any fluid?

DR HANELIN No.

DR HAMLIN We have to cling to straws. I do not think there is much value in discussing what a large irregular mass, felt suprapubically and in the posterior cul-de-sac, might be, because as far as I am concerned at the moment it could be anything. There is only one item that, if true, might be of some help (otherwise, fibroids would be far and away the most likely diagnosis) that is the statement made by the patient that the mass "swelled intermittently." It is not carefully stated what relation this had to the uterus.

DR CASTLEMAN Do you know, Dr Sturgis?

DR SOMERS STURGIS No.

DR HAMLIN Therefore, the field is wide open. We can guess about anything we want to. There is nothing outside the realm of possibility. It need not have anything to do with the pelvic organs. Let us look at it from the point of view of trying to correlate the pain in the chest with a mass in the pelvis. We immediately think of Meigs-Cass syndrome†. That, of course, involves ascites and pleural fluid, but neither, apparently, was present here.

The next thing one thinks of is a pulmonary infarct. Infarct could clear up in this period. It is possible that the patient would have had an infarct to account for the pain in the chest, but that does not help a bit.

DR CASTLEMAN Excuse me, Dr Hamlin, I have just found a little more information.

DR HAMLIN I thought there would be.

DR CASTLEMAN The record states "On bimanual pelvic examination the lesion seems to incorporate the uterus and movement of the mass is transmitted to the cervix."

DR HAMLIN Reward for being overcautious! We then think of metastases. There is no x-ray evidence of metastases. Metastases to lung or pleura, I think, we can ignore for lack of evidence. I want very much to work in perihepatitis. I took occasion to look up perihepatitis in relation to pelvic disease but could not find anything about it, although it certainly was taught when I was a house officer that it was common in association with salpingitis and we certainly do see many cases accompanied by a perihepatitis. It may simulate gall-bladder disease on occasion and produce the typical

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knocked out by metastatic carcinoma — a rather frequent event in carcinoma of the bronchus

On the whole it seems to me that the odds are in favor of the tumor's being in the stomach, and I have not got the courage to put it anywhere else in the face of positive gastric washings. I have raised a number of questions that I cannot answer intelligently, but since I have to take a stand of some sort I will say that this man had arteriosclerotic heart disease and cor pulmonale, probably on the basis of many small emboli, and carcinoma of the stomach with metastases

DR ALFRED KRANES I wonder if the pulmonary metastases may not have been tumor emboli, and if that was so, I think it is not impossible that carcinoma of the pancreas might produce that picture

DR BRAILEY I should have mentioned that, but tumor emboli occur in carcinoma of the stomach too

DR KRANES But much less commonly, I believe

DR BRAILEY That is right

DR BLAND Does carcinoma of the bronchus frequently metastasize to the supraclavicular lymph nodes?

DR DONALD S KING Quite commonly

DR MALLORY Dr Warthin, I believe you were interested in this case

DR THOMAS WARTHIN I saw this patient in the Out Patient Department and was struck by the fact that he had heart disease basically. He definitely had abnormal lymph nodes, one of which was characteristic of the Virchow type associated with carcinoma of the stomach. Now seeing the x-ray films, which I had not seen before, I consider them typical of lymphogenous spread of carcinoma of the stomach, such as has been described by Mueller and Sniffen* from this hospital

DR BLAND Would sarcoid cause this picture in the lung?

DR KING It could, my opinion is that this was not sarcoid

CLINICAL DIAGNOSES

Congestive heart failure
Arteriosclerotic heart disease
Carcinoma of stomach?
Pulmonary metastases?

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Generalized thrombosis of small pulmonary arteries Cor pulmonale

PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed that this man had a cor pulmonale. The wall of the right ventricle measured 7 mm in thickness, the left ventricle was normal. The lungs showed diffuse involvement of all the lymphatics with tumor. In a search for the source of the tumor an ulcerated lesion was found in the stomach. A large mass of tumor was found in the region of the pancreas, which at the time of autopsy was interpreted as lymph nodes surrounding the pancreas rather than a primary tumor of the pancreas itself. The subsequent microscopical examination showed that the acinar cells of the pancreas were totally replaced by tumor from end to end of the organ, and I believe that was the primary site. Invasion of the stomach was secondary, but since the secondary tumor had ulcerated into the lumen there is no reason why tumor cells should not be found in the gastric washings. On microscopical examination of the lungs it became evident that nearly all the arteries were surrounded by dilated lymphatics filled with tumor cells and that the majority of them also contained organized thrombi. In only a small number of vessels were tumor cells present within the intra-arterial thrombi, so that tumor embolism was unimportant.

There is no way that I can say from the anatomical findings whether the arterial thromboses, which were old enough to be completely organized, were independent of the carcinoma or secondary to it. I am inclined to think it was secondary, but I cannot prove the point.

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DR MALLORY Pulmonary lymphatics in normal conditions are so collapsed that they are scarcely visible. In this lung an artery was surrounded by four or five lymphatics, each so distended with tumor as to be of diameter equal to that of the artery.

CASE 35442

PRESENTATION OF CASE

A forty-six-year-old housewife was seen in the Out Patient Department complaining of pain under the right breast.

She was perfectly well until one month before admission, when after a particularly hard day's work a "catching" pain appeared in the right side of the

chest, increasing on deep inspiration. The pain persisted for several weeks and then slowly subsided. There was no cough, sputum, hemoptysis, nausea, vomiting or weight loss. Three weeks before admission, while in Canada on a vacation, she consulted a physician. After fluoroscopic examination she was told that she had pleurisy. She received pills for pain and returned home. Since then she was up and around doing housework. During the year before admission she noted a lump in the suprapubic region that swelled intermittently.

At the age of eighteen she had "wet pleurisy" on the right side and was treated at home by a homeopathic physician. Her father and mother were alive and well. Two of nine siblings had died of tuberculosis, but the patient had had no contact with them. An aunt and cousin had died of cancer.

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CASE 35442

PRESENTATION OF CASE

A forty-six-year-old housewife was seen in the Out Patient Department complaining of pain under the right breast.

She was perfectly well until one month before admission, when after a particularly hard day's work a "catching" pain appeared in the right side of the

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THE CONTINUING CHALLENGE OF PULMONARY EMBOLISM

AFTER World War I it was noted that post-operative pulmonary embolism was on the increase. To be sure, some of this was only apparent because of the better recognition of the condition both clinically and post mortem. An actual increase was, however, accepted and was variously ascribed to exhaustion and poor health resulting from the war, to the increasing age of patients subjected to surgery, and to the bolder operative procedures that improvement in anesthesia and surgical technics made possible in patients who would previously have been considered poor risks. It is quite probable that the last two factors as well as better recognition of the condition by internist, surgeon and pathologist alike accounted for the increasing awareness of this threat. The same reasons may still apply today,

as well as others not yet defined favoring an increased amount of thromboembolic disease.

As time went on it also became obvious that pulmonary embolism was much more common in medical patients than had been thought this important complication had been previously in many cases called something else, in particular hypostatic pneumonia or pulmonary edema due to heart failure.

Thus it was only natural that during the last decade vigorous action should have been taken to try to prevent pulmonary embolism which was often fatal after serious surgical operations and which was also one of the commonest causes of death in cases of chronic cardiac disease. Various measures were introduced to curb the threat. Two of the simplest and perhaps the best have been early mobilization after surgery and the use of penicillin to help to make such mobilization possible. Stasis favoring thrombosis in the leg veins, the commonest cause of pulmonary embolism was thus minimized. Also efforts were made to reduce pressures and positions causing stasis during surgical operations themselves and to ease the strain of bowel movements, to reduce "bedpan death."

Two special measures, which were widely introduced to limit the hazard of pulmonary embolism and which have had their vigorous proponents, have been the use of anticoagulants and ligation of the femoral veins both as prophylaxis and as treatment. Statistics have been presented to indicate the value of both methods in a more or less parallel fashion, and many individual cases have been known and some reported in which the institution of either or both of these therapies has apparently been life saving. But there have been failures, too, often not so distinctly delineated.

In the present issue of the *Journal* an interesting and important experience of the Department of Pathology of the Massachusetts General Hospital is presented. Despite the institution of the measures cited above during the five-year period from 1943 to 1947 inclusive, there was a definite increase in the notation of fatal pulmonary embolism found at autopsy over that in two previous five-year periods, 1931 to 1935 inclusive, and 1936 to 1940 inclusive (442 per cent of 2083 autopsies in 1943

violin-string type of adhesions That would be a tempting choice here except that it is extremely hard to envisage a salpingitis as large as this mass apparently was It is possible certainly, although I have never seen a pelvic mass as large as this due entirely to salpingitis

We come to the other straw here—namely, a great deal of talk that makes one think of tuberculosis, which is mentioned in the past history and which did not have to be mentioned Two siblings had tuberculosis, and it would seem that that at least is something we should try to work together I do not pretend to know very much about pulmonary tuberculosis The patient certainly had old scarring in the lungs It would seem to me that if she had tuberculous pleurisy on this occasion, it had cleared up very rapidly It is possible that she had mild pleurisy associated with it

How would that fit with the pelvic mass? Tuberculosis of the pelvis is not uncommon in relation to tuberculous salpingitis and endometritis, but again a mass of this size would seem quite unusual This would be easy if we could put in one or two other diagnoses such as concomitant fibroids

One thing that occurs to me is a cold abscess It seems unlikely, but it interests me a good deal I do not know why I thought of cold abscess in this case I have not seen one for a long, long time The fact that this mass varied in size and perhaps the description that Dr Castleman just gave—the uterus being incorporated in the mass—suggest a large cold abscess filling the cul-de-sac and emerging suprapubically

I do not like to bet very heavily on any of the possibilities I have mentioned I am sure there are plenty of others, but since one has to go out on a limb, I may as well make it a long limb and say that this woman had a tuberculous abscess

DR CASTLEMAN Does anyone else want to go out on a longer limb?

DR STURGIS Could Dr Hamlin amplify the statement about intermittent swelling?

DR HAMLIN I simply mentioned that in thinking of a cystic mass instead of a solid mass We have no description to indicate that it was cystic or solid I carefully did not ask for that because I did not want to hear that it was solid

DR STURGIS Is there any chance of digging out anything from the record in reference to the menstrual cycle? I wonder if endometriosis might come in as a vague possibility

DR HAMLIN It certainly could I think the fact that any reference to the menstrual cycle was carefully omitted made me ignore that possibility

DR CASTLEMAN I note in the record that the patient stated that the mass seemed to swell and become tender with her menstrual periods

DR HAMLIN I believe you can see the justification for my remarks when I began

DR ALLEN G BRAILEY Would Dr Hamlin consider Meigs-Cass disease?

DR HAMLIN I did and discarded it because of lack of described ascites

DR JACOB LERMAN Does the fluid in Meigs-Cass syndrome disappear rapidly?

DR CASTLEMAN The Meigs-Cass syndrome is a condition in which a fibroma of the ovary is associated with ascites and pleural fluid Some years ago Drs Meigs and Cass reported a group of these cases The pleural fluid does not reaccumulate after the ovarian tumor has been removed, I believe it is resorbed so slowly that, in most cases, it is removed by paracentesis

CLINICAL DIAGNOSIS

Fibroid uterus

DR HAMLIN'S DIAGNOSIS

Tuberculous abscess of pelvis

ANATOMICAL DIAGNOSES

Tuberculous salpingitis, endometritis, and peritonitis

Leiomyomas of uterus

PATHOLOGICAL DISCUSSION

DR CASTLEMAN Dr Hamlin's limb was pretty good, in spite of all the handicaps, unintentional as they were The large mass that was felt was the ordinary leiomyomatous uterus, but associated with it, on the serosal surface of the uterus, as well as on the tubes, ovaries and peritoneum, were very small, grayish nodules At the time of operation the surgeon thought they might possibly be carcinomatous Our microscopical sections proved that they were all tuberculous and that this patient had tuberculous salpingitis, endometritis and peritonitis, the peritonitis being present all over the pelvic cavity as well as on the surface of the appendix It is quite possible, although it was not explored, that she had a perihepatitis as a result of salpingitis The surgeon removed the uterus and both tubes but left the ovaries The tuberculosis appeared quite active, and I imagine that the patient has been sent to a sanatorium

notable also for restraint and factual basis. For its content of good sense, though not comparable to the first as a product of research, "Changing Concepts in Posture Training," by L. W. Irwin³ should also be mentioned.

But the collection of the last seven years includes much that must be discarded by the critical reader. Some of this material in the hands of unprotected parents seems almost certain to lead to improper care of children, and it is regrettable that it should receive the prestige of publication. These pages contain dogmatic instructions concerning the baby's standing and sitting habits, and especially his sleeping posture, which must be followed or deformity is said to result. It is indeed surprising that no attempt has yet been made to correct the posture of the fetus in utero. This somewhat cloistered stage of development certainly defies all the rules of the posturites, and for a time that seems long enough to lead to a permanent deformity if a cramped position for a sustained period can deform. There is room for doubt that even if a baby insists upon sleeping on his chin, to mention one practice strongly decried by these writers, such a position necessarily leads to deformity. A more important basis for fear is the menace to mother-child relations of constant nagging correction of such a habit in baby or child.

In appraising the posture of the school child it is apparent to many that unlovely slouches or slumps are more apt to be the result than the cause of ill health. It is apparent also that spontaneous correction occurs in the vast majority of school children when no true structural deformity exists. In view of this spontaneous tendency to correction, one is led to doubt the value of special corrective exercises as provided by some schools, especially if they include separation into special classes. The possibility exists that special classes themselves may lead to social maladjustment.

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CHEST X-RAY PROGRAM—A REPORT OF PROGRESS

THE Boston Chest X-Ray Program, as of October 14, reported that 139,442 x-ray films had been taken, of which 99,939 had been processed. This encouraging beginning has been made in only eighteen operating days.

An analysis of the practically 100,000 processed films shows that 95.63 per cent were negative and 1891, or 1.89 per cent, gave some evidence of disease. Definite tuberculosis was evident in 826 cases and suspected tuberculosis in 489. Nontuberculous chest disease appeared on 360 films, and cardiovascular disease on 216.

The Committee on Nontuberculous Chest Disease, a subcommittee of the Medical Committee of the Program, is naturally concerned about the treatment and disposal of patients in whom chest disease of a nontuberculous nature is found, and has suggested procedures pertaining to their care.

These recommendations point out that cancer is the most important diagnosis to be considered in the evaluation of nontuberculous pulmonary disease, and emphasize the criteria necessary for its identification, as well as the necessity for rapid processing of films in order to facilitate early diagnosis. Particularly stressed are the definition of those lesions that should cause the patient to be designated as a cancer suspect, and the further management of such cases.

Suitable orientation of physicians in this regard is important in that all cases of nontuberculous pulmonary disease discovered will be referred back to the family doctor or to the Massachusetts Medical Society for advice if there is no family physician, but private care is desired. Other patients will be referred to established thoracic clinics in or near Boston.

One of the most persistently discouraging facts about cancer of the lung, as demonstrated by Overholt and Schmidt,* is the long interval of ten months that elapses, on the average, between the patient's first visit to the doctor and the time when the diagnosis is made. The lessons to be learned from the Boston Chest X-Ray Program should be of value in cutting down this "tragic interlude."

*Overholt, R. H. and Schmidt, I. C. Survival in primary carcinoma of lung. *New Eng J Med* 240:491-497 1949

to 1947 as compared to 2.16 per cent of 1991 in 1931 to 1935 and 3.66 per cent of 1832 in 1936 to 1940). This finding is, at first thought, discouraging and even appalling, and most certainly presents a continuing challenge, but there are certain features whose consideration is necessary before final conclusions are drawn.

In the first place the actual incidence of unquestioned fatal pulmonary embolism in patients whose femoral veins were bilaterally ligated either prophylactically (4) or therapeutically (6) was only 0.5 per cent (10 patients out of 1929 cases so treated). There was another group of 11 cases with smaller emboli after the ligation, making a total of 21, or 1.1 per cent. Four other patients had their veins ligated *after* embolism that subsequently proved to be fatal. One other had an embolus consisting of a renal-cell carcinoma. This leaves a balance of 63 cases with fatal pulmonary embolism, 14 with large, possibly fatal embolism, and 105 with small emboli who did not have leg-vein ligation, a total of 182 as compared with 21 who did have the ligation. One would, of course, like to know how many patients there were who were comparably ill or operated upon (not just total admissions) of whom these 182 made a part. It is quite possible that the ratio of pulmonary embolism might be found to be higher in that group than in those subjected to ligation, as data already published from the Massachusetts General Hospital have indicated.¹⁻³ This analysis, though difficult, would be well worth while in amplifying the data already presented. Incidentally, it is of much interest and doubtless of considerable importance to note the fact that, on the average, the patients admitted to the hospital in the last five-year period—that is, from 1943 to 1947 inclusive—were eight years older than those admitted in the first period, 1931 to 1935 inclusive. In addition, it has been stated that a diminished mortality from shock, infection and pneumonia in recent years has put thromboembolic disease more in the limelight.

However, even if ligation and anticoagulant therapy (800 cases received Dicumarol at the Massachusetts General Hospital during 1947 alone but were not analyzed in this report) reduce the threat of pulmonary embolism, as has been the experience

of most surgeons and internists, they are not yet good enough since death can occur despite them as clearly shown by the paper of Roe and Goldthwait in the individual case reports, several of which revealed thrombi in the veins proximal to (that is, nearer the heart than) the ligation site. Moreover, these measures have not, in all probability, been applied to enough cases or always in adequate degree to obtain the best results. Finally, the high percentage of unanticipated, fatal pulmonary embolism in this series is rather surprising especially in a hospital where the staff has presumably been on the alert, this fact simply indicates the need of still more attention to this frequent complication both postoperatively and in medical patients.

Thus, the challenge of pulmonary embolism still exists in major form.

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FURTHER PSEUDODOXIA

THE "total health of the child" is a popular present-day concept, which hardly any physician contemplates without comprehension of the importance of child happiness and the security of his family relations. It is well that this should be so. However, this relatively new recognition of the importance of mental hygiene is likely to uncover practices that although dimly recognized as unsatisfactory, have not hitherto seemed enough of a menace to health to warrant serious attention. Some of these practices were mentioned by Bakwin¹ in 1945 as "pseudodoxia pediatrica," and among them is also the pseudoauthoritative writing that is found in some of the semiofficial and voluntary journals upon the subject of posture. A review of the literature of the last seven years reveals some strictly scientific articles on the posture of the child, among which should be mentioned, "New Approach to Quantitative Analysis of Children's Posture" by Robinow, Leonard and Anderson.² This, with its many illustrations, has a highly instructive value and is

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CHANGES IN ACT FURTHER PROVIDING FOR THE CARE OF CERTAIN INFANTS

Changes in the law relating to the care of premature infants enacted by the General Court (Chapter 601 Acts of 1949) became effective on October 25, 1949. The responsibilities for the care of premature infants formerly allocated to local boards of welfare are now transferred to local boards of health. This transfer is made because this is primarily a matter pertaining to health and also because of the hope that it will remove the welfare stigma that has interfered with the full use of legal provisions in the past. Many families who could afford to pay for hospitalization of ordinary length find it impossible to meet the cost of the prolonged periods sometimes necessary for premature infants. It is the purpose of this legislation to help such cases.

The changes in Chapter 601 are outlined as follows:

Administration

Local boards of health or local health jurisdictions rather than local boards of welfare, are now responsible for the administration of this law.

Weight

Defined as $5\frac{1}{2}$ pounds or less at birth, instead of 5 pounds or less, to conform to federal and other state definitions.

Reporting of Premature Births

By hospital — to the local board of health or local health jurisdiction of the town where the mother resides instead of the local board of welfare of the town where the infant is born.

By physicians (for premature births outside hospitals) — to the local board of health or local health jurisdiction of the town where the infant is born instead of to both boards of health and welfare.

Payment for Hospitalization

Only for infants weighing $4\frac{1}{2}$ pounds or less at birth (if parents are unable to pay).

By local health agency — by local board of health or local health jurisdiction instead of by local board of welfare of the town of mother's residence. If the mother's settlement is in another town the board of health of the town of settlement will reimburse the board of health of the town of residence on written notification within sixty days.

No expense shall be reimbursed that was incurred more than ten days (instead of five) prior to receipt of original notice sent to local board of health.

Ceiling rates for hospitalization are established by the Massachusetts Department of Public Health.

By Massachusetts Department of Public Health — for cases with no legal settlement, hospitalization will be paid by the Massachusetts Department of Public Health.

Copies of the Act are being sent to all physicians, hospitals, boards of health, boards of welfare, public-health nursing organizations and others interested.

Attention is called to the importance of acquainting parents who may need financial assistance with the provisions of this act.

CORRESPONDENCE

ON THE HEATING OF INFANT FORMULAS

To the Editor — In the article by Drs. Joseph C. Merriam and C. G. Tedeschi which appeared in the August 25 issue of the *Journal*, the results of terminal heating of infant formulas under steam pressure were discussed. The conclusion was reached that although terminal heating at 15 pounds of pressure for five minutes or at 6 pounds for ten minutes produces bacteriologically safe products, there are some undesirable side effects in the form of coagulum in the formula and sticking of the nipple shields to the nipples. Reference is made to the New York State Sanitary Code, Chapter II, Regulation 35 as the source of these recommended procedures.

The terminal heating requirements of Regulation 35 are based on the experience of Cummings in the Michigan State Health Department, on the recommendations of the subcommittee of the American Hospital Association which made a study of terminal heating of formulas on extensive studies made in the New York State Department of Health and on suggestions submitted by hospitals in New York State at the time Regulation 35 was in preparation. Two of the three methods have been adopted by the American Academy of Pediatrics.

There is a wide experience in the use of all three methods of terminal heating. The success that one hospital has with a given method may not be duplicated in another hospital. This may be attributable to differences in formula, to differences in the heating efficiency of the equipment in use and to the human factors of careless timing and failure to remove the formula from the autoclave as soon as possible. Small bottles filled too full often result in nipple plugging. In general, the Department of Health personnel are in favor of lower temperatures for terminal heating of formulas. The requirement of 250° for five minutes was included in the regulation as a permissive provision at the request of certain hospitals that were using this method prior to the adoption of Regulation 35. In view of the fact that autoclaves can be equipped with an attachment that will make it possible to operate them at any one of the three temperatures allowable under Regulation 35, this regulation is applicable in any hospital. It is recommended that hospitals experiment with a few formulas in adequate size bottles until they find the method that seems best suited to their personnel and their types of formula. Since all hospitals in New York State are now carrying out terminal heating of formulas and many of them are using steam pressure, the formation of coagulum and the sticking of nipple shields to nipples do not seem to constitute a universal problem.

The bacteriologic results mentioned by Drs. Merriam and Tedeschi are parallel to those obtained in the New York State Department of Health and by others who have studied this problem.

These few comments have been submitted in an effort to clarify any misunderstanding that might arise concerning the practicability of the requirements of the New York State Sanitary Code for the terminal heating of infant formulas.

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The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

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This honorary volume was issued in commemoration of the sixtieth birthday of Dr. George R. Mino in 1945. One hundred and fifty-five colleagues and friends of Dr. Mino contributed eighty-three articles on the blood and related

TALE OF TWO CITIES

Old ways are best in Budapest, according to observations recently published by Suranyi.* The infant mortality in the twin cities had reached the deplorable level of 269 per 1000 in July and August of 1945, in the corresponding months of 1948 it had dropped to 57. The reason given for the improvement was a health campaign in which breast feeding was emphasized, aided in a practical manner by the application of short-wave therapy to the breasts. Ten such treatments, it is said, resulted in a prolonged 50 per cent increase in milk excretion in a third of the cases.

Figures indicate that up to 4,166,500 gm of human milk have been collected and dispensed in one month through the 19 centers that have been established in the city. An average of 2500 infants per month have received the benefits of this service, preference being given to premature and sick babies. During a test period the mortality rate among infants receiving the breast milk was 36 per 1000, as against a rate for the city as a whole of 79 per 1000.

Like Horace's Spartans, the women of Hungary seem to have opposed to the strokes of adversity their gallant breasts.

*Suranyi G. I problemi dell'alimentazione del lattante e la loro soluzione a Budapest. *Il Lattante* 20:129-139, 1949.

AMERICAN ACADEMY OF PEDIATRICS

The annual meeting of the American Academy of Pediatrics, which will be held at the Palace Hotel in San Francisco from November 12 to 17, promises to be of great interest to all pediatricians as well as the many general practitioners whose practice includes pediatric cases. The program consists of seminars, original papers and round-table and panel discussions on the various pathologic conditions and infections encountered in infancy and childhood, attention will also be given to mental, emotional and endocrine problems.

This congress marks the eighteenth annual convocation of the Academy. The publication of the results of the surveys on child health services in various states^{1, 2} lends added significance to the

meeting of the organization primarily responsible for this investigation. The *Journal* wishes the Academy every success in the various surveys and in the continued efforts to solve the problems of child health in the United States.

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A hundred years hence, some philanthropist will probably deplore the gullibility of civilized man in whatever pertains to his individual health. While the elements of humanity remain as they are, there will be no lack of cheats and impostors, and the pleasure of being cheated will continue to be as great as when Butler wrote his Hudibras.

Boston M & S J, October 31, 1849

MASSACHUSETTS MEDICAL SOCIETY



DEATHS

GARDNER — Edwin D. Gardner, M.D., of Marion, died on October 12. He was in his sixty-fifth year.

Dr. Gardner received his degree from Harvard Medical School in 1910. He was former chief of surgery at St. Luke's Hospital, and was chief of the surgical staff of Tohey Hospital, Wareham. He was a member of the American Urological Association and a fellow of the American College of Surgeons and American Medical Association.

His widow and two sisters survive.

HATT — Rafe Nelson Hatt, M.D., of Honolulu, Hawaii, died on May 27. He was in his sixtieth year.

Dr. Hatt received his degree from Tufts College Medical School in 1918. He was formerly chief surgeon at the Shriners' Hospital for Crippled Children, Springfield, and consulting orthopedic surgeon at Springfield and Wesson Memorial hospitals. He was a past president of the Springfield Academy of Medicine and was a nonresident member of the Massachusetts Medical Society. He was a member of the American Orthopaedic Association and the American Academy of Orthopaedic Surgeons and a fellow of the American College of Surgeons.

His widow, a son, two daughters and a granddaughter survive.

WATTERS — William H. Watters, M.D., of Boston, died on October 11. He was in his seventy-fourth year.

Dr. Watters received his degree from Boston University School of Medicine in 1900. He was professor emeritus of preventive medicine at Boston University School of Medicine and was a member of the American College of Physicians and a fellow of the American Medical Association.

His widow survives.

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George R. Minot Symposium on Hematology, By William Dameshek, M.D. and F. H. L. Taylor, Ph.D., editors. 4°, cloth 984 pp. with illustrations and tables. New York: Grune and Stratton, 1949. \$12.00.

This honorary volume was issued in commemoration of the sixtieth birthday of Dr. George R. Minot in 1945. One hundred and fifty-five colleagues and friends of Dr. Minot contributed eighty-three articles on the blood and related

subjects. The articles were originally published in *Blood* during 1948 and 1949, and are here brought together in one volume as a "Festschrift" through the generous financial support of the Lederle Laboratories and Mr J K Lilly. The text is preceded by a full-page portrait of Dr Minot and by his biographic data. The first article is a reprint from the *Journal of the American Medical Association* of August 14, 1926. This article, "Treatment of Pernicious Anemia by a Special Diet," which was by Dr Minot and Dr William P Murphy, represented the outstanding contribution of these two physicians and won them the Nobel prize. The text is divided into seven parts into which the various articles are classified: pernicious anemia, hemolytic anemia, anemia other than pernicious or hemolytic, blood-clotting phenomena and hemorrhagic disease, leukemia, biologic and cytologic reactions of blood and blood-forming tissues, subdivided into red cells, white cells, blood-forming organs and certain biochemical aspects, and general practice, containing two contributions on peptic ulcer and on diabetic coma. There are indexes of authors and subjects.

The original article of Minot and Murphy has long been out of print and is made available in this volume. The book is recommended to all medical libraries.

NOTICES

ANNOUNCEMENTS

Dr Robert J Fahey announces the opening of offices for the practice of internal medicine at 119 High Street, Medford, and 520 Commonwealth Avenue, Boston.

Dr A William Reggio announces the change of his address from 2301 Connecticut Avenue, N W, Washington, D C, to School Street, Medfield, Massachusetts.

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 15, at 12 noon. The speaker will be Dr Hans Waine, medical director of the New England Chapter of The Arthritis and Rheumatism Foundation, who will discuss arthritis and rheumatism, and especially Cortisone, the new treatment for these diseases.

Physicians are cordially invited to attend.

GREATER BOSTON ASSOCIATION OF MEDICAL TECHNOLOGISTS

A meeting of the Greater Boston Association of Medical Technologists will be held at the Nurses Home of the New England Baptist Hospital, on Tuesday, November 8, at 7 30 p m. Dr Donald A Nickerson will speak on the subject "Evaluation of Blood Sugar Technics."

NEW ENGLAND CARDIOVASCULAR SOCIETY

The following scientific program of the New England Cardiovascular Society for 1949-1950 has been announced (all meetings will be held on Monday evenings at 8 15).

November 7 Massachusetts General Hospital Edward Bland, M D, chairman

December 5 Peter Bent Brigham Hospital, Samuel Levine, M D, chairman

January 9 Boston City Hospital Laurence B Ellis, M D, chairman

February 6 Massachusetts Memorial Hospitals Robert W Wilkins, M D, chairman

March 6 Beth Israel Hospital Herrman Blumgart, M D, chairman

April 3 Children's Medical Center (House of the Good Samaritan and Children's Hospital) Benedict F Massell, M D, chairman

May 8 Annual meeting

Members who wish to give papers and are staff members of hospitals in which no meeting has been scheduled are requested to submit papers to the Secretary (Dr Benedict F Massell). If sufficient papers are submitted, an additional meeting will be arranged.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3-MAY 19 Massachusetts Department of Mental Health Postgraduate Seminar in Neurology and Psychiatry Page 286 issue of August 18

NOVEMBER 6 AND 7 American Society for the Study of Arteriosclerosis Page 594, issue of October 13

NOVEMBER 7 New England Cardiovascular Society Page 678, issue of October 27

NOVEMBER 7-9 National Society for Crippled Children and Adults Page 184 issue of July 28

NOVEMBER 7-12 International College of Surgeons. Page 251, issue of August 11

NOVEMBER 8 New England Society of Anesthesiologists Page 630, issue of October 20

NOVEMBER 8 Edward K. Dunham Lecture Page 678, issue of October 27

NOVEMBER 8 Greater Boston Association of Medical Technologists. Notice above

NOVEMBER 8-10 Salmon Memorial Lectures Page 594 issue of October 13

NOVEMBER 10 Human Streptococcosis. Dr Louis Weinstein. Perinatal Association of Physicians. 8 30 p m. Haverhill

NOVEMBER 10 Edward K. Dunham Lecture Page 678 issue of October 27

NOVEMBER 14-17 American Academy of Pediatrics Page 251 issue of August 11

NOVEMBER 15 South End Medical Club Notice above.

NOVEMBER 16 Massachusetts State Society of Examining Physicians. Page 324 issue of August 25

NOVEMBER 23 Pediatric Seminar for Physicians and General Practitioners. Page 550, issue of October 6

(Notices concluded on page xiii)



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And knows all the wherefores and whys*

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CARCINOMA OF THE EYELID*

Analysis of 301 Cases and Review of the Literature

CHARLES G. STETSON, M.D.,† AND MILFORD D. SCHULZ, M.D.‡

BOSTON

THE treatment of carcinoma of the eyelid presents many problems not encountered in the treatment of similar lesions elsewhere about the face and other body surfaces. A satisfactory cosmetic result is imperative, and the likelihood of disaster after delayed, inept or unsuccessful treatment is considerable. Several excellent studies have been carried out on this subject, and all workers of considerable experience have reported poor results in patients who have presented themselves with recurrent or persistent disease following previous therapy in other hands. The purpose of this paper is to evaluate the various methods of treatment of primary carcinoma of the eyelid by examination of locally available clinical material and by a review of the experience of others as recorded in the literature.

Carcinoma of the eyelid, like carcinoma of the skin elsewhere, is not a rare disease, occurring more commonly in the male than in the female, and increasing in incidence with age. Different authors have listed chronic irritation, sunlight, chemical irritants, old scars and precursory keratoses as the etiologic factors with about the same conviction as in cancer of the skin on other parts of the body.

The course of the disease is variable. Basal-cell lesions of the eyelid, as in other areas, invade and destroy adjacent tissue by direct extension, but they do not metastasize. Serious sequelae may ensue, however, from their extension from the lid to adjacent structures. Involvement of the bulbar conjunctiva with subsequent destruction of the globe may result and in cases in which there has been extension into the orbit, incurable involvement of the bony orbit may occur. Lesions about the inner canthus frequently invade the lachrymal duct and

may extend directly into the ethmoid sinuses. Hunt¹ states that basal-cell carcinoma of the lid may travel along lymphatics, penetrate the orbital fascia and give rise to orbital extension. Birge² found that 25.9 per cent of the basal-cell cases and 6.8 per cent of the mixed group extended into the orbit with ensuing blindness, all the latter group originated at the inner canthus.

Squamous-cell lesions of the eyelid not only spread by direct extension, giving rise to the complication of orbital and sinus invasion, globe destruction and bony involvement characteristic of an untreated basal-cell carcinoma, but also tend to metastasize to the orbit and regional lymph nodes. Birge² found that the conjunctiva was involved in 37 per cent of his squamous-cell lesions of the eyelid and that orbital extension almost always accompanied conjunctival and corneal involvement. Hunt¹ reported that 2 of 10 cases metastasized to regional lymph nodes and that the upper and outer lid lesions tended to spread to the preauricular nodes and lesions of the lower lid to the upper cervical nodes. In Martin's³ experience, the preauricular node is the common site of involvement.

The ultimate course of the disease, like cancer of the skin everywhere, depends in a large part upon its stage of advancement when treatment is undertaken and to a lesser degree upon its location. Small lesions, and others not so small that have not invaded the orbit or sinuses and have not seriously damaged the globe, may be controlled without significant deformity. Uncontrolled lesions may result in the loss of an eye and even in eventual death, owing to local extension or to metastasis in cases of squamous-cell carcinoma. Birge² found that the most important factor in prognosis of a basal-cell lesion is its location. In his opinion, cancer of the eyelid is an extremely serious condition because of its ability to blind and kill. He considers the basal-cell lesion a worse "killer" than the squamous-cell lesion, the inner canthus and upper lid to be associated with the greatest mortality, and the

*From the Department of Radiology and the Tumor Clinic of the Massachusetts General Hospital.

Presented at a meeting of the New England Cancer Society, November 5, 1948.

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chance of cure to be negligible if the disease has extended into the orbit. In his series, the mortality from basal-cell lesions was 11 per cent, and that of the entire group of cancer of the eyelid was 12 per cent. His experience with squamous-cell lesions has been wider than that of the other workers cited, and his observations therefore carry weight. In the group of cases with squamous-cell carcinoma of the eyelid the grade of malignancy and the clinical behavior correlated well, the greater the malignancy, the greater the tendency to involvement of lymph node or orbit. Grade IV lesions had the highest death rate, whereas Grade II and III had the highest over-all mortality because of their greater incidence. In Grade I lesions there were no deaths and no loss of the eye. Lesions of the inner canthus proved nearly as dangerous as those of the upper lid.

Martin³ found a mortality of 6 per cent in his group, the adenoid cystic epithelioma being more malignant than other types as well as being a potentially metastasizing lesion.

MATERIAL

The clinical material for this study consists of the

workers Birge,² in whose series the average duration was over one year, believes that the majority of lesions develop over a long period. Charters⁴ reported a duration of disease from two months to twenty years, and in Hunt's¹ group, 30 per cent of patients had had the disease for over three years.

Age and Sex

Sixty per cent of the lesions occurred in males. The median age of the group was fifty-eight, the youngest being twenty and the oldest eighty-nine. Seventy-five per cent of the group were between fifty and seventy-nine years of age, the peak falling in the sixth decade. If correction is made for normal population decay, however, the incidence is found to increase in a linear fashion after the age of forty.

Incidence of Eyelid Involvement Among All Carcinomas of Skin

During the twelve-year period under consideration, approximately 12,000 cases of cancer of the skin were observed, making the incidence of eyelid involvement 2.5 per cent. Birge² reported that cutaneous cancer represented 12 per cent of all

TABLE 1 Topographic Distribution of Lesions

AUTHOR	LESIONS OF LOWER EYELID	LESIONS OF INNER CANTHUS	LESIONS OF UPPER EYELID	LESIONS OF OUTER CANTHUS	COMBINATIONS	OTHERS	TOTALS
Stetson and Schulz	145 (48.2%)	63 (21.0%)	44 (14.6%)	27 (9.0%)	22 (7.2%)	—	301
Martin ³	80 (54.0%)	41 (28.0%)	19 (13.0%)	7 (5.0%)	—	—	147
Birge ²	107 (46.5%)	54 (23.4%)	29 (12.6%)	20 (8.7%)	—	—	230
Lane ⁵	149 (46.5%)	90 (18.0%)	52 (10.4%)	32 (6.4%)	89 (18.0%)	20 (8.7%)	500
Hollander and Krugh ⁷	47 (37.6%)	52 (41.5%)	17 (13.5%)	9 (7.2%)	—	—	125
Driver and Cole ⁸	164 (50.0%)	86 (25.0%)	30 (10.0%)	21 (6.0%)	23 (8.0%)	—	324
Charters ⁴	19 (18.5%)	61 (58.0%)	9 (8.5%)	16 (15.0%)	—	—	105
Hunt ¹	48 (48.0%)	34 (34.0%)	6 (6.0%)	12 (12.0%)	—	—	100
Totals	759 (42.0%)	481 (26.0%)	206 (11.0%)	144 (8.0%)	134 (7.0%)	108 (6.0%)	1,832

hospital records of 301 patients with primary carcinoma of the eye who were seen in the clinics of the Massachusetts General Hospital and of the Collis P. Huntington Memorial Hospital during the twelve-year period from January, 1933, through December, 1944. Only cases in which the carcinoma was primary in the eyelid and in which no previous treatment had been given were included, in all but 1 case the lesions were confined to the eyelid and immediately contiguous structures. Inasmuch as 86 per cent of all recurrences develop within three years of treatment, this particular period was selected so that the minimal follow-up interval would be that in which the recurrence of disease might be expected.

Duration of Disease

The average recognized duration of the disease in the group was three and a half years, the shortest period was one month, and the longest twenty years. This is in fair agreement with the findings of other

epitheliomas, and that 3 to 5 per cent of these were located on the eyelid. The group of 324 carcinomas of the eyelid studied by Driver and Cole⁸ constituted 16.8 per cent of 1925 epitheliomas of the skin seen in their clinic.

Topographic Distribution of Lesions

The lower lid was the most frequent site of involvement (48.2 per cent), and the inner canthus the second most common site (21.0 per cent). The upper lid and outer canthus follow in frequency of occurrence, 14.6 and 9.0 per cent respectively (Table 1). In 22 patients (7.2 per cent), several areas on the lids in the same patient were involved. Six patients exhibited two separate lesions, 3 with bilateral lesions and 3 with the two separate lesions on the same side. In Birge's series, 37 per cent of the squamous-cell cancers arose from the conjunctival surface, including the cornea, primary corneal squamous-cell neoplasm was rare.

Histology of Lesions

The diagnosis in 162 cases (54 per cent of the entire group) was confirmed by biopsy, in the remaining 139 cases the diagnosis was clinical only, the lesions bearing the expected characteristics of basal and squamous-cell carcinoma. Of the 162 histologically proved cancers (Table 2 and 3), 82 per cent were basal-cell (4 of the hair-matrix type), 14.5 per cent squamous-cell, and 2.4 per cent basal-

cell type group who had been followed three years or longer, since it was found that in 86 per cent a recurrence, if there were one, developed within three years. Figure 1 and 2 demonstrate the results in 2 cases eight and twelve years, respectively, after treatment. Of the 21 cases in which there was a recurrence of disease, it appeared within a year in 38 per cent, between one and two years in 24 per cent, and between two and three years in 24 per cent. In 2 cases the disease recurred in the

TABLE 2 Histopathological Classification of Lesions

AUTHOR	TOTAL NO. OF CASES	LESIONS BIOPSED	BASAL-CELL LESIONS	MIXED LESIONS	SQUAMOUS CELL LESIONS					ADENOID CYSTIC LESIONS	OTHERS
					TOTALS	GRADE I	GRADE II	GRADE III	GRADE IV	LY- GRADED	
Stetson and Schulz	301	162 (54.0%)	133 (82.0%)	4 (2.4%)	23 (14.5%)	18	11	3	—	—	—
Birge ²	464	230 (49.5%)	139 (60.0%)	32 (14.0%)	59 (25.0%)	8	21	18	6	6	—
Narun ³	147	—	125 (85.0%)	—	15 (10.0%)	—	—	—	—	—	—
Hollander and Krugh ⁴	125	60 (48.0%)	45 (75.0%)	1 (1.6%)	13 (21.6%)	—	—	—	—	—	—
Driver and Cole ⁵	324	109 (33.6%)	73 (66.0%)	9 (8.2%)	20 (18.2%)	—	—	—	—	—	—
Hunt ¹	100	61 (61.0%)	48 (78.7%)	3 (4.9%)	10 (16.4%)	—	—	—	—	—	—

cell and squamous-cell lesions, and 1.2 per cent adenoïd cystic epitheliomas. Rare carcinomas arising in meibomian glands have been reported by Hagedoorn⁶ and Lebensohn⁷, none were observed in this series. Neither in the present group nor in the cases reported by Birge² or Hunt¹ did there seem to be any predilection of site for any particular type of tumor.

Treatment and Results

In 76 per cent of the entire group, irradiation treatment was used. The majority of 23 patients

fourth year, and in only 1 was the recurrence as long as the fifth year after treatment. The average follow-up period was six and three-tenths years.

The results of treatment were classified as follows: "cure" from primary treatment, "cure" after subsequent treatment, and failure (from recurrent disease, from persistent disease and from metastasis). The term "cure" is applied to cases in which there was no apparent disease during the follow-up period. "Recurrent disease" indicates recurrence in a previously treated area after an interval of at least three months following therapy during which

TABLE 3 Histopathological Distribution of Lesions

SITE OF TUMOR	TOTAL NO. OF CASES	BASAL CELL CARCINOMAS			MIXED CARCINOMAS			SQUAMOUS CELL CARCINOMAS			ADENOID CYSTIC CARCINOMAS		
		STETSON AND SCHULZ	BIRGE ²	HUNT ¹	STETSON AND SCHULZ	BIRGE ²	HUNT ¹	STETSON AND SCHULZ	BIRGE ²	HUNT ¹	STETSON AND SCHULZ	BIRGE ²	HUNT ¹
ALL TYPES	453	162	230	61	—	—	—	—	—	—	—	—	—
Lower eyelid	213	65	76	20	1	14	2	10	17	6	2	—	—
Inner canthus	108	25	37	20	2	9	1	4	8	—	—	—	—
Upper eyelid	60	24	14	—	1	5	—	6	10	2	—	—	—
Outer canthus	38	7	12	5	—	4	—	1	4	—	—	—	—
Combinations	14	12	—	—	—	—	—	2	—	—	—	—	—
Others	20	—	—	—	—	—	—	—	20	—	—	—	—
Totals	453	162 (35.8%)	230 (50.8%)	61 (13.4%)	4 (0.9%)	32 (7.1%)	3 (0.7%)	23 (5.1%)	59 (13.0%)	10 (2.2%)	2 (0.4%)	—	—

treated with 100 kv r received a single large dose. Of the 111 treated with 200 kv, 75 per cent were given a single large dose, and 25 per cent fractionated doses. The effective tumor dose was about 3000 r. When radon was applied topically, the average skin dose was 3275 gamma r. Seventy-one patients were treated surgically (electrosurgery or surgical excision).

Table 4 records the methods and results of treatment. The results are based on patients of the en-

tire group who had been followed three years or longer, since it was found that in 86 per cent a recurrence, if there were one, developed within three years.

From a percentage standpoint, no significant difference was noted in the number of failures of the various treatments employed. In an attempt to determine the causes of the unsatisfactory results of the primary treatment, it was found that inadequate radiation, or inadequate excision in patients treated surgically, headed the list. In 5

cases failure was due in part to error in x-ray technic (the size of the field was inadequate to cover the lesion) In 6 of the surgically treated cases, inadequate excision was demonstrated by recurrence of the disease in the suture line The tumor proved radioresistant in 11 cases, — for example, a superficial lesion 0.5 cm in diameter did not respond to

CASE 1 An uncontrolled recurrence in a 79-year-old man resulted from inadequate excision of an 0.5 cm basal-cell lesion of the upper eyelid The recurrent growth, which developed 5 months after excision, was re-excised and showed a mixed squamous-cell and basal-cell tumor The disease then extended into the orbit and was treated with 200 kv x-ray This was classed as a surgical failure (The patient died 3 years after the first excision from rupture of multiple hemangiomas of the gastrointestinal tract.)

TABLE 4 Methods of Treatment and Comparative Results in 219 Cases Followed

TREATMENT	TOTAL NO TREATED	CURES*			FAILURES			
		BY PRIMARY TREATMENT	AFTER SECONDARY TREATMENT	TOTALS	TOTAL NO	RECURRENT DISEASE	PERSISTENT DISEASE	METASTATIC DISEASE
Radon	25	22	3	25 (100%)	0	0	0	0
Radium	3	2	1	3 (100%)	0	0	0	0
X-ray (100 kv)	23	20	3	23 (100%)	0	0	0	0
X-ray (200 kv)	111	96	11	107 (97%)	4 (3.0%)	0	3	1
Surgery	57	50	6	56 (99%)	1 (1.0%)	1	0	0
Totals	219	190	24	214 (97.5%)	5 (2.5%)	1	3	1

*No evidence of disease after treatment for the period of follow-up study

a single dose of 3000 r (air) In one case the appearance of metastases accounted for failure, another failure was due to the fact that at the time the patient was first seen the disease had extended into the bony orbit

From the standpoint of topographic distribution, there was nothing to indicate that the position of

CASE 2 A 69-year-old man presented total involvement of all lids, globe and orbit at the time of his initial visit. Biopsy revealed a squamous-cell cancer, Grade III He received fractionated daily 200 kv x-ray therapy, to a field 10 by 10 cm, a total dose of 3000 r measured in air being given He refused further treatment He was known to be living five years after treatment and was assumed to have residual disease In all probability the disease was incurable at the time he was first seen, but adequate palliation was obtained

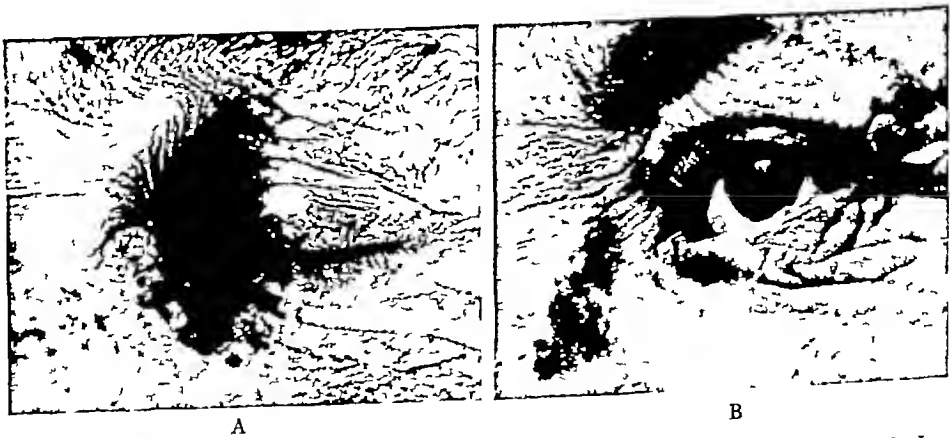


FIGURE 1 Photographs of Patient J. J. (U-328878), with a Basal-Cell Carcinoma about the Inner Canthus Involving the Punctum, Who Was Treated with 500 r per Day for 3500 r with 200-kv, 0.25-mm Copper Filter at a Skin-Target Distance of 20 cm

A shows the lesion before treatment, and B three years after treatment The patient was well and free of disease eight years after treatment, with only slight tearing as an undesirable complication

the lesion had any bearing on an unsatisfactory result, provided the disease had not already become uncontrollable because of extension to lymph nodes, the orbit or the sinuses The histologic characteristics of the tumor, however, appeared to be of significance Failure of the primary treatment was twice as frequent in squamous-cell lesions as in basal-cell lesions The 5 cases that were ultimate failures are briefly reported as follows

CASE 3 A 54-year-old man had persistent uncontrolled disease from an 0.5-cm basal-cell carcinoma at the inner canthus He refused to accept more than a single treatment, and was given 3500 r (air), 200 kv x-rays with 0.25-mm Cu and 1-mm Al filters being used Nine months later, when he was persuaded to return to the clinic, there was clinical evidence of residual disease The final outcome is unknown since the patient refused both further treatment and further follow-up study

CASE 4 An 84-year-old, extremely feeble woman had a squamous-cell carcinoma, Grade III, involving the entire

lower lid. She refused hospitalization, and was treated with x-rays generated at 200 kv, filtered with 0.25 mm Cu and 1 mm Al. At weekly intervals 400 r, measured in air, was given to a total dose of 1200 r (air). The patient was unable to return for further treatment because of increasing feebleness and died from bronchopneumonia 5 months from the date of her initial visit. She might have been cured.

CASE 5 A 57-year-old man died from metastatic disease from a Grade I squamous-cell lesion on the outer aspect of the upper lid. The primary cancer was destroyed by daily

treatment and 68 or 89 ± per cent with good results from the primary treatment.

Richards¹⁰ had 3 failures out of 102 cases treated, in 2 of the failures previous treatment had been given. Martin⁸ did not find five-year results revealing, he believed that the end-results must be evaluated on the basis of function and appearance. In 85 per cent of his patients the first treatment was



FIGURE 2 Photographs of Patient A S (U-346117), with a Squamous-Cell Carcinoma Involving the Inner Canthus and Punctum, who was Given a Single Treatment of 2000 r with 200-kv, 0.25-mm Copper Filter at a Skin-Target Distance of 20 cm.

A shows the appearance before treatment, and B three years after treatment. The patient was well twelve years after treatment with only slight telangiectatic formation at the lid margin.

treatments of 600 r (a r) to a total dose of 4200 r (air), 200 kv x-ray therapy with 0.25-mm Cu, 1-mm Al filters at skin-target distance of 50 cm being used. Eight months later, adenopathy of the upper cervical lymph nodes on the side of the original lesion developed, biopsy showed metastatic squamous-cell carcinoma. The metastases were considered to be too extensive for a radical neck dissection, particularly as the patient was a poor surgical risk. The nodes were irradiated with 200 kv, but the patient went downhill rapidly and died 18 months after the initial treatment to the eyelid. This case might have been salvaged had the cervical involvement been noted at an earlier date.

The results of treatment in this study are not comparable to those of other workers, since only patients who received their primary treatment in this clinic were included. It is interesting to note, however, that good results in the treatment of this disease have been reported by most of the clinics whose work has been published. Hollander and Krugh⁷ had good results in 97 of 125 cases and unsatisfactory results in 28, they concluded that no method of treatment is superior to any other.

Driver and Cole,⁵ in a follow-up study of 291 patients for one month or over, found 19 (6.5 per cent) recurrences and 272 (93.5 per cent) possible cures. There were 6 deaths from the disease. Among 193 cases followed for six months to ten years there were 12 relapses. Relapses after five years were rare, 181 cases, or 93.8 per cent, were possible permanent cures.

In 76 cases treated with radium, Charteris⁴ reported 2 failures, 6 patients requiring secondary

successful, 7 per cent required more than one treatment, and 6 per cent died of their disease.

Birge² followed 127 of 139 basal-cell carcinomas of the eyelid and found an 11 per cent mortality. In the basal-cell group, 46.1 per cent of patients lived fifteen years or more, 75 per cent with the mixed type of carcinoma lived fifteen years or longer. Of the squamous-cell cancers, 50 per cent recurred, Grade III showing the greatest tendency to recurrence. There were no deaths in the Grade I (squamous-cell) group, 15 per cent of patients with Grade II lesions died, and among those with Grade III tumors there was a 46 per cent death rate. The orbit was involved in 30 per cent of the Grade II squamous-cell group and in 53 per cent of Grade III, in Grade IV, the orbit was invaded in every case and no patient survived five years.

COMPLICATIONS OF TREATMENT

Complications of treatment of carcinoma of the eyelid — that is, undesirable by-effects incident to treatment that would otherwise have been considered satisfactory — are not numerous. Complications that follow surgical treatment are primarily unsightly scars or defects requiring plastic revision and lid-drop due to interference with the innervation or attachment of the elevator of the lid. Among 71 patients treated by means of surgical operation, 1 case of each of these complications occurred.

Undesirable side effects are more common after irradiation. The most frequent of these is stenosis of the tear duct when lesions involving the inner canthus and medial portions of the lids are treated. Out of 31 cases in which the inner canthus was irradiated, stenosis of the tear duct developed in 8, or 26 per cent. This complication is at times unavoidable, especially when the neoplasm has already invaded and destroyed the duct. Since lesions in this location do not lend themselves to surgical intervention, a certain number of stenosed ducts must be expected and accepted as the legitimate price paid for control of the disease.

It is the opinion of some investigators that attempts should be made to dilate and keep open the stenosed and destroyed duct. This procedure, however, is of benefit only in cases in which the stenosis is not complete and in which the duct has not been entirely destroyed by tumor.

The formation of cataract is a serious post-radiation complication and has often been reported. It should never occur, however, when the lesion is treated with x-rays and the globe has been properly protected with a lead shield. Protection of the lens when radium is used is difficult. In our series no case of radiation cataract has been observed. This is accounted for in part by the fact that the eye has always been carefully shielded during x-ray therapy. Radium and radon have been employed only in a limited and selected group of patients. A radium plaque was used once, interstitial radium needles three times, and interstitial radon seeds on two occasions, and in 35 other cases surface application of radon was utilized for superficial lesions, the average skin dose not exceeding 3300 r.

Several interesting observations have recently been reported concerning the time factor in the development of radiation cataract and the amount of radiation necessary to produce it. Hunt¹ found the average latent period to be twelve years, although the complication might develop in three months. He reported 5 cases in which lens opacities developed, 2 from radium and 3 from unshielded x-ray therapy (there were none in the shielded cases). He calculated the dose received by the lens in the 3 cases treated by radium to be 2400, 1500 and 1350 r, the opacities developing after six months, eight years and five years respectively. Of the 2 opacities that followed x-ray therapy, the dose in 1 was 875 r (air), 130-Kv x-ray, 1-mm Al filter, and in the other 4800 r in 6 treatments from 130-kv x-ray, 1-mm Al filter, both were unshielded.

Martin² states that cataracts may develop in twelve to thirty-six months after radiation. In Smithers's¹¹ experience, a five-year latent period is not uncommon. Charteris⁴ believes that eye damage is unlikely if the dose is below 2800 r although it may follow 1500 r. He found the implantation of radium to be most dangerous when applied to an upper-lid lesion. Of his 76 patients treated by

radium, 11 showed late ocular changes, 7 of which he attributed to radiation (4 lost their vision). Richards¹⁰ believes that cataract develops only as a result of long-continued use of hard rays.

In our opinion proper care and meticulous attention to details of technic when carcinoma of the eyelid is treated by x-rays should eliminate this hazard completely, except in cases in which extensive tumor involvement of the orbit and globe makes it impossible to protect the eye itself. In the 2 patients in the present series in whom destruction of the globe, subsequently necessitating enucleation, occurred there was extensive involvement of the bulbar conjunctiva at the time the patient was first seen, making protection of the eye impossible.

Persistent chronic, painful conjunctivitis following x-ray treatment has been observed only once in this group. Corneal ulcer, a theoretical complication of radiation, has never been seen. Proper protection of the globe and careful shielding of the adjacent normal tissues with lead should allow irradiation without damage to bulbar conjunctiva or cornea.

Severe deformity of the lids requiring plastic repair, observed in only 3 of the cases treated by radiation, occurs only when the disease is advanced and there is already destruction of tissue by tumor.

DISCUSSION

Good results in the treatment of carcinoma of the eyelid can be obtained by any of the available methods in skilled hands. Prior to any form of treatment, after the diagnosis has been established, the patient should have a thorough examination by a competent ophthalmologist. It is important to have a record of these findings in the event of subsequent ocular complications. In all fixed lesions about the lid, adequate x-ray studies of the sinuses and orbit, to rule out possible bony involvement, should be made. This is particularly necessary in infiltrating and fixed lesions about the inner canthus, which are prone to extend into the ethmoid sinuses; it is mandatory in cases in which the globe or orbital tissues are invaded by disease.

A capable plastic surgeon may obtain good results by the excision of small lesions. Against this choice of treatment stands the fact that there is often considerable nonvisible tumor infiltration, which results in recurrence of tumor in the suture line. Surgery plays an important role in a selected number of patients who have extensive involvement of the globe or orbit. Radical exenteration of the orbit may be required, the globe as well as other orbital tissues must be removed in case of involvement. When residual disease is suspected, radiation to the orbit should follow surgical operation.

Prior to the acquisition of suitable low-voltage therapy, most of the superficial lesions of the eyelid were treated by surface application of radon. Only limited use has been made of surface and interstitial

therapy with radium element. At the present time the routine use of radium with its possible sequelae does not seem justified when equally good results can be obtained with roentgen-ray therapy without the danger of damage to the eye.

If x-radiation is to be employed, the first consideration is protection of the eye. For low-voltage x-ray treatment Hunt¹ used a 12-mm lead shield coated with nickel. He found that a 1-mm lead shield removed 97 per cent of the radiation from 140-kv x-rays, filtered with 0.25-mm Cu and 1-mm Al. Smithers¹¹ points out that complete protection is impossible when the tumor has invaded the eyeball or orbit and states that the risk of damage to the eye from treatment must be considered as of secondary importance. When the tumor is limited to the lid, he uses for low-voltage therapy an accurately ground contact glass lens covered by 1 mm of lead. He states that less than half of 1 per cent of low-voltage radiation will penetrate this shield. He also describes a very practical type of plastic Perspex eyeshield covered by 1 mm of lead, this is available in multiple sizes and contours. Driver and Cole⁶ prefer lead shields coated by paraffin.

For the treatment of most primary carcinomas of the eyelid x-ray therapy seems to be the method of choice. The occurrence of failures or other undesirable results is no greater than with other forms of therapy, the discomfort to the patient is not great, and the cosmetic and functional results are equal to or better than those obtained by other means. An accepted technic of procedure, found to be satisfactory, is described below.

Technic of Irradiation of Eyelid

The eyeball is anesthetized, and a 2-mm lead shield coated with paraffin is inserted. The size of the shield is adequate to include a margin of normal surrounding tissue. An excellent protective device for lesions of the inner canthus is a lead nipple shield (Fig 3C). These nipple shields are no longer available commercially, but they can be easily made.

For small lesions, x-rays at 100 kv, unfiltered, with a skin-target distance of 20 cm are used. A single treatment of 2700 to 3000 r (air) may be delivered, or the fractionated technic may be employed. It is thought that the latter gives better cosmetic results. For the treatment of a small lesion with the fractionated method, daily doses of 1200 to 1500 r (air) are given to a total of 3600 to 4500 r (air). When the lesion is more extensive the daily dose may be reduced to 500 r (air) and carried to a total dose of 5000 to 6000 r (air).

For treatment of an infiltrating and fixed lesion, particularly one in the region of the inner canthus, 140-kv to 200-kv x-rays filtered by 0.25-mm Cu and 1-mm Al are used. The treatment is fractionated.

For a lesion that has involved the bony orbit or ethmoid sinus by extension, 200-kv x-rays with 0.5-mm Cu and 1-mm Al filters are employed.

Experience with Phillips contact therapy has not been of sufficient duration to evaluate results. It appears to have a definite place in the therapeutic armamentarium available for the treatment

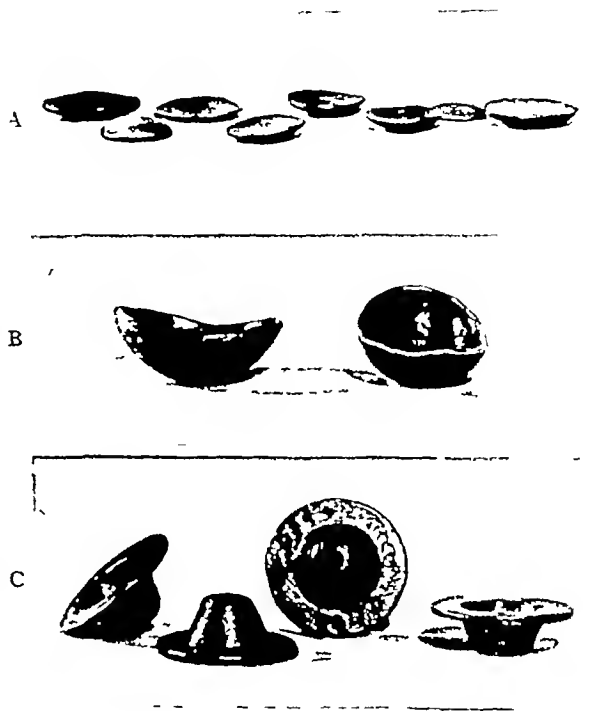


FIGURE 3 Protective Shields for Lesions of the Inner Canthus. A shows various sizes and shapes of paraffin-covered lead shields, designed to fit beneath the lid and over the globe. These are made by hammering of pieces of lead, 2 mm thick, between the ball and peen of a mechanic's hammer. B illustrates larger lead shields, designed to fit over the lid and globe of the eye and made in essentially the same manner. C shows old-fashioned lead nipple shields, with holes of various sizes bored in their tips, used in the treatment of lesions about the inner canthus.

of carcinoma of the eyelid although its use should probably be reserved for superficial lesions.

SUMMARY AND CONCLUSIONS

The experience with treatment of carcinoma of the eyelid at the Massachusetts General Hospital and at the Collis P. Huntington Memorial Hospital during the twelve-year period from 1933 through 1944 is summarized, and the pertinent literature is reviewed.

The study was based on 301 cases of primary carcinoma of the eyelid having an average duration of three and a half years. Sixty per cent of the lesions occurred in males, the median age of the patients was fifty-eight years. Carcinoma of the eyelid

represented an incidence of 2.5 per cent of all skin cancers observed during the same period.

The lower lid was the most frequent site of involvement, the inner canthus was the second most common. Histologic examination showed that 82 per cent of the biopsied lesions were basal-cell carcinomas, 14.5 per cent were squamous-cell tumors.

The methods and the results of treatment are analyzed, 76 per cent of patients received irradiation, and 24 per cent were treated by surgical procedures. Evaluation of the results of treatment has been based on the group of cases in which the follow-up period was three years or longer, primary failure to control the disease was manifest within three years in 86 per cent of the group. Apparent cures were ultimately obtained in 97.5 per cent of the cases. Failures from the initial treatment, however, occurred in 13 per cent, all these 29 lesions were controlled by subsequent management except 5. The secondary treatment in most cases was not the same as the primary treatment had been. The net failures comprised 2.5 per cent of the cases.

From a percentage standpoint there was nothing to indicate that the method of treatment influenced the end-results. These results have been compared with those previously published by other workers.

The chief complications of treatment were scars and defects from surgical operation requiring plastic revision and stenosis of the tear duct following radiation therapy of lesions involving the inner canthus. No cases of radiation cataract have been encountered in this clinic.

The available methods of treatment of carcinoma of the eyelid are discussed, and the technic of x-ray therapy employed at the Massachusetts General Hospital outlined.

Primary carcinoma of the eyelid when limited to the lid has an excellent prognosis if the treatment is adequate. Even in the event of initial failure to control the disease, subsequent treatment is usually successful.

Squamous-cell carcinoma of the eyelid is more refractory to treatment and results in more complications than basal-cell carcinoma, and therefore has a poorer prognosis.

In the treatment of primary carcinoma of the eyelid, good results can be obtained by any of the available methods of treatment judiciously applied. The facility of treatment by x-radiation and the excellent cosmetic and functional results that usually follow make it, as a rule, the treatment of choice.

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CHLOROMYCETIN IN THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN*

A Preliminary Report on Thirty-Three Cases

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CHLOROMYCETIN is an antibiotic derived from a strain of *Streptomyces venezuelae*. Its antimicrobial spectrum is broad and embraces the following organisms: rickettsia, certain viruses of the psittacosis group, gram-positive cocci (including the pneumococcus, streptococcus and staphylococcus) and certain gram-negative organisms including *Eberthella typhosa*, shigella and several of the coliform group.¹ The drug is well tolerated orally, and few toxic reactions have followed its use in therapeutic doses. Chloromycetin is readily absorbed after oral administration, and blood levels of 10 to 40 mg per 100 cc are readily obtained when 50 to 100 mg per kilogram of body weight are administered daily to children in a four-hour to six-hour divided-dosage schedule.² The drug is also absorbed moderately well after rectal administration, the level, to a first approximation, representing 20 to 50 per cent of the absorption obtained after oral administration.² In view of the insolubility of chloromycetin in water or saline solution, parenteral administration of the drug is not feasible.

The sensitivities to chloromycetin of the pneumococcus, streptococcus, staphylococcus and *Haemophilus influenzae* have been found in vitro to range between 0.5 to 5 microgm per cubic centimeter—concentrations that are readily exceeded with therapeutic doses of the drug orally. Since these organisms constitute the most common etiologic agents of bacterial pneumonia in infants and children a clinical trial of the drug in the disease appeared to be indicated. Thus, during the winter of 1948-1949, a special pneumonia ward was set up at the Children's Hospital, Washington, D C to study the efficacy of chloromycetin (as well as aureomycin) in the treatment of pneumonia. During a four-month period, 39 patients were treated with aureomycin,³ and 33 with chloromycetin. The present report deals with the results obtained in the latter group.

METHOD OF STUDY

A uniform diagnostic workup was employed in each suspected case of pneumonia. This consisted of an x-ray examination of the chest, complete blood count, nasopharyngeal and blood cultures and agglutinins for streptococcus MG and cold hemagglutinins. After this initial study, repeat chest films, blood counts and nasopharyngeal cultures were taken every two or three days during the course of therapy, and the serologic studies were performed at intervals of seven to fourteen days. Strict clinical and laboratory criteria were employed before a case was included in this study, and any patient who presented equivocal findings on admission was summarily excluded from this series.

Thirty-three patients fulfilling the established diagnostic requirements of pneumonia were treated with chloromycetin. The ages of these children ranged from four months to twelve years. Of these, 3 patients were less than six months, and 6 ranged from six to twelve months, 8 from one to two years, 5 from two to six years, and 11 from six to twelve years of age.

The 33 cases in this series, all of which were considered to be bacterial pneumonias, were classified as follows: pneumococcal 18, streptococcal 1, staphylococcal 1, and unclassified, 13. A pneumococcus was the sole or predominating organism on the nasopharyngeal cultures of the first group, a finding that was considered strong evidence that this organism represented the pathogen in the lower respiratory tract. Beta-hemolytic streptococci in large numbers were cultured from the nasopharynx of 1 patient, and *Staphylococcus aureus* was isolated from the throat and empyema fluid of another. Nasopharyngeal cultures in the other 13 cases of pneumonia yielded *Staph aureus*, *Staph albus*, *Streptococcus viridans*, *Neisseria catarrhalis* and *H influenzae*, and the cases were therefore placed in the unclassified group. This is predicated on the fact that, with the exception of the pneumococcus, the isolation of an organism from the nasopharynx is not necessarily presumptive evidence that it represents the pathogen in the lower respiratory tract.⁴ It is possible that in several of the unclassified group, the organism isolated on nasopharyngeal culture was indeed the cause of the pneumonia, particularly in the 4 cases in which

*From the Research Foundation, Children's Hospital. This study was supported by a grant to the Children's Hospital from the Antibiotic Study Section of the Division of Research Grants and Fellowships, The National Institutes of Health, United States Public Health Service, and was conducted under the auspices of the Antibiotic Committee of Children's Hospital consisting of Drs. E. Clarence Rice, Frederic G. Burke and John A. Washington.

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H influenzae was the predominant organism. However, definite proof was lacking, and thus the unclassified group constitutes a singularly large percentage of the total number of cases. In spite of the inability to indict a specific organism as the causative agent, the clinical manifestations together with the roentgenologic findings and leukocytosis were all compatible with a diagnosis of bacterial pneumonia in this unclassified group.

Twenty of the 33 patients were considered to be markedly ill at the time of admission, and 8 of these required oxygen. Eleven of the remaining 13 were regarded as moderately ill, and the other 2 cases were classified as mild. The temperature at the time of initiation of chloromycetin therapy ranged from 101 to 106°F. In 27 of the 33 cases, it was above 103°F. In 16 patients (48 per cent) the white-cell count at the time of hospitalization was above 20,000, and in 15 cases it ranged from 10,000 to 20,000. Two other patients showed white-cell counts below 10,000. In each patient in this series there was demonstrable x-ray evidence of pneumonia.

DOSAGE OF CHLOROMYCETIN

Chloromycetin* was administered orally in a dosage ranging from 50 to 220 mg per kilogram of body weight per twenty-four hours, or an average of 112 mg per kilogram per day. The dosage in-

TABLE 1 Results in 33 Cases of Bacterial Pneumonia Treated with Chloromycetin

TYPE OF PNEUMONIA	GOOD RESULTS	FAIR RESULTS	NO EFFECT
	NO OF CASES	NO OF CASES	NO OF CASES
Pneumococcal	13	5	—
Streptococcal	1	—	1
Staphylococcal	11	2	—
Unclassified	—	—	—
Totals	25	7	1

terval was usually every three hours, an occasional patient receiving the drug every four hours. The duration of therapy ranged from two to six days, with an average of four and eight-tenths days per patient. The total dose of chloromycetin ranged from 3.4 to 11.3 gm, with an average of 5.9 gm per patient.

With reference to the administration of chloromycetin orally, only in the older age group was it possible to administer an intact capsule. In infants and younger children, it was necessary to empty the contents of the capsule and, in view of the extreme bitterness of the drug, to administer it in different vehicles. These included syrup of Santa Yerba, chocolate milk, chocolate syrup,

cherry syrup, applesauce and lemon juice. Our experience in this regard indicated that mixing the drug with syrup of Santa Yerba and following it with chocolate milk was perhaps the best method of administration in small children.

RESULTS

The therapeutic effect of chloromycetin on the 33 patients with bacterial pneumonia was favorable. The over-all results (based principally on the rapidity of return to normal of clinical, roentgenologic and laboratory findings) were considered good in 25 cases, fair in 7 and poor in only 1 (Table 1). In 1 case a relapse occurred a week after the drug had been discontinued, and the patient was retreated with chloromycetin. An uneventful recovery ensued. One patient who had a staphylococcal pneumonia with an associated empyema showed no improvement with chloromycetin after forty-eight hours. Penicillin and aureomycin were then substituted, but the patient failed to improve until surgical drainage was performed.

In 20 of the 33 patients the temperature returned to normal within eighteen hours of the initiation of chloromycetin therapy (Fig 1). In 7 other patients defervescence was observed eighteen to thirty-six hours after treatment had been started. In 5 of the 6 remaining cases, the temperature was normal after thirty-six to seventy-two hours. Thus, in 32 of the 33 cases, the temperature was normal within three days of the initiation of therapy. Concomitantly, there was striking clinical improvement characterized by prompt relief of the prostration, dyspnea and cough.

The rapidity of clearing of the nasopharyngeal pathogens following initiation of chloromycetin was observed by the performance of serial nasopharyngeal cultures on each patient. The first culture was obtained at the time of admission, and two to four subsequent cultures were obtained at two-day intervals. In 9 of the 18 cases of pneumococcal pneumonia, the organism was not demonstrable after the second day of therapy. In 2 other patients, the organisms had disappeared by the fourth day. In the remaining 7, pneumococci (usually in reduced number) were still demonstrable on nasopharyngeal culture after the fourth day. Of the 4 cases in which *H influenzae* was the predominant organism on the initial culture, 3 were negative for this organism two days after chloromycetin therapy had been started. In the case in which a hemolytic streptococcus was the sole organism isolated from the nasopharynx prior to treatment, the organism disappeared two days after therapy had been begun.

An analysis of the drop in white-cell counts revealed that in 21 of the 33 patients the count had returned to normal by the third day after the initiation of chloromycetin therapy. Of ancillary interest was the observation that in several cases

*Supplied by Parke-Davis Company, Detroit, Michigan, through the courtesy of Dr. E. A. Sharp.

the white-cell count dropped below 4000 three to five days after therapy had been started. However, the leukopenia was not progressive and was not associated with any granulocytopenia. In no case was it necessary to discontinue the drug because

Chloromycetin was discontinued after 4½ days, and the patient was discharged on the 7th hospital day after an uneventful recovery. Figure 2 shows the course in the hospital.

He was examined in the follow-up clinic 2 weeks after leaving the hospital and found to be in good condition. Repeat cold hemagglutinins and streptococcus MG titers at this time were negative.

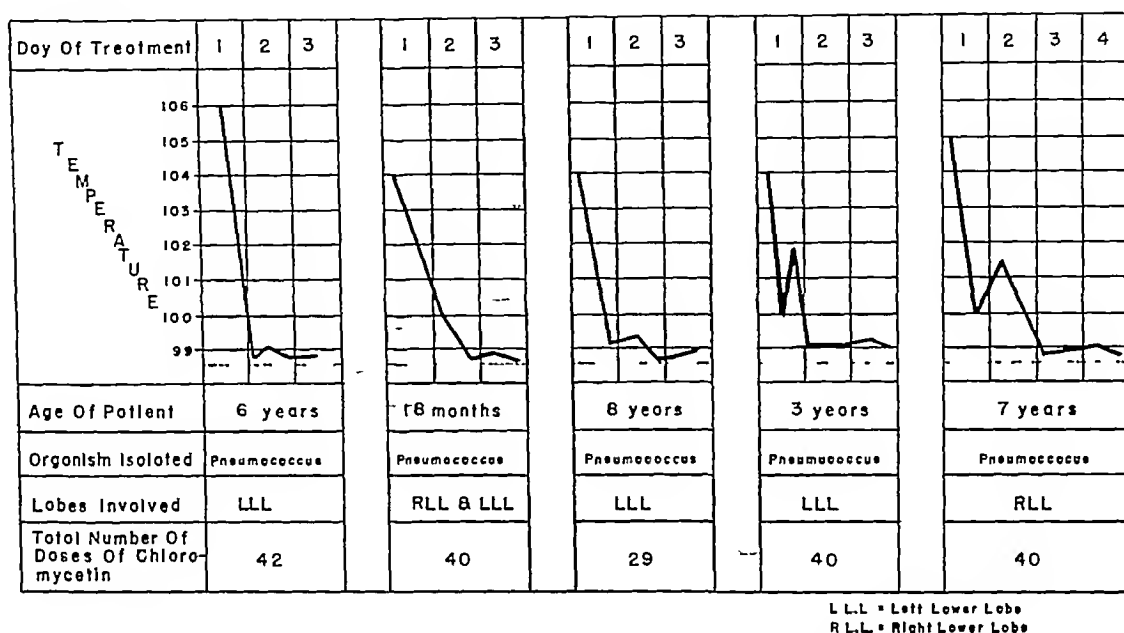


FIGURE 1 Representative Cases of Pneumococcal Pneumonia Treated with Chloromycetin

of the leukopenia. There was no concomitant reduction in red-cell or platelet count.

Serial chest x-ray films showed appreciable resolution of the inflammatory process four to seven days after chloromycetin had been started in 24 out of the 33 patients.

Data on the therapy and results in 18 cases of pneumonia are presented in Table 2. The following cases serve to illustrate the response to chloromycetin.

T.E., an 11-month-old Negro boy, was admitted to the hospital with a 2-day history of fever, progressive cough and rhinorrhea.

Physical examination revealed an acutely ill and dyspneic infant with a temperature of 104°F by rectum. Fine crackling rales were heard in the right axilla and over the right lower portion of the chest posteriorly. The remainder of the examination was essentially negative.

The white-cell count on admission was 15,400, with 73 per cent neutrophils. Beta-hemolytic streptococci were cultured from the nasopharynx. A blood culture was sterile. Cold hemagglutinins and streptococcus MG titers were negative. X-ray study of the chest disclosed a disseminated area of infiltration in the right-lung field.

Chloromycetin therapy was instituted on admission in a dose of 250 mg initially followed by 125 mg every 3 hours. The infant improved rapidly, and in 12 hours was afebrile and considerably improved clinically. The white-cell count dropped very quickly, on the 2nd day it was 6000, with 40 per cent neutrophils, and on the 5th day it was 3700 with 22 per cent neutrophils. Nasopharyngeal cultures on the 3rd and 6th days yielded no pathogens. Repeat chest x-ray examination on the 5th day revealed no appreciable resolu-

R.J., a 2-year-old Negro boy, had had a high fever, cough and anorexia 2 days before entry. These symptoms progressed during the next 48 hours, at which time hospitalization was advised.

Physical examination revealed an acutely ill child with a temperature of 104.6°F by rectum, a pulse of 136 and res-

TABLE 2 Data in 18 Cases of Pneumococcal Pneumonia Treated with Chloromycetin

Case No.	Age	CHLOROMYCETIN THERAPY			Result
		DAY INITIATED	DOSE mg/kg/24 hr	TOTAL DAYS	
1	5 yr	2	83	3	Good
2	1	2/12	83	4	Fair
3	1	2/12	168	6	Fair
4	5	7/12	212	5	Good
5	7	7/12	84	5	Good
6	1	7/12	106	5	Good
7	1	6/12	88	5	Good
8	12	6	50	5	Good
9	8	4	55	6	Good
10	8/12	3	125	5	Good
11	6	3	115	6	Good
12	3	2	107	5	Good
13	5/12	2	220	5	Fair
14	7/12	3	102	6	Fair
15	1	11/12	100	5	Good
16	6	6	210	4	Good
17	3	5	132	5	Good
18	4/12	4	200	6	Fair

pirations of 72 per minute. The pharynx and the right eardrum were injected. Over the left posterior portion of the chest there were dullness to percussion, increased breath sounds and fine crepitant rales on auscultation.

X-ray study of the chest disclosed a diffuse inflammatory process throughout most of the left lung indicative of bronchopneumonia.

Pneumococci were isolated from the nasopharynx, and a blood culture was sterile. The white-cell count on admission was 24,400, with 90 per cent neutrophils. Cold hemagglutinins were present in a dilution of 1:128, and streptococcus MG agglutinins in a dilution of 1:10.

The patient was placed in an oxygen tent, and chloromycetin therapy was promptly begun in a dosage of 250 mg initially followed by 125 mg every 3 hours. Clinically, the child improved rapidly and was out of the oxygen tent in 24 hours and afebrile in 36 hours. Follow-up nasopharyngeal cultures failed to grow out pneumococci. There was con-

pneumonia treated with aureomycin or chloromycetin an attempt was made at the conclusion of the study to compare the efficacy of the two drugs in the disease.

There were 18 patients with pneumococcal pneumonia who received chloromycetin, and 11 who

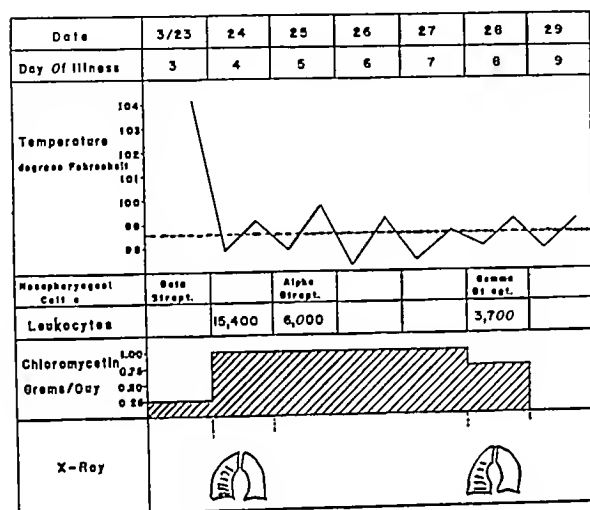


FIGURE 2 Results of Chloromycetin Therapy in T. E.

siderable clearing of the area of infiltration on x-ray examination within 3 days and complete resolution in 6 days. The white-cell count returned to normal in 3 days.

Chloromycetin was discontinued after 4 days, and the patient was discharged in good condition on the 8th day.

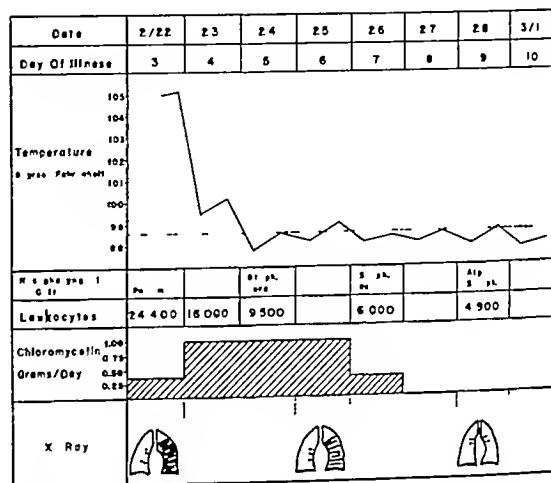


FIGURE 3 Results of Chloromycetin Therapy in R. J.

were given aureomycin orally. In both groups the age range, the duration of illness prior to the initiation of therapy and the severity of the illness were quite comparable (Table 3). On the average, the patients treated with chloromycetin received a larger dose approximating 25 mg per kilogram of body weight per dose. The disparity was rather empirical since the optimal dose of both drugs for children has not as yet been conclusively worked

TABLE 3 Comparison of the Therapeutic Efficacy of Aureomycin and That of Chloromycetin in Pneumococcal Pneumonia

DRUG	NO OF PATIENTS	AVERAGE AGE	AVERAGE DURATION OF ILLNESS BEFORE TREATMENT	MAXIMUM TEMPERATURE	AVERAGE MAXIMUM WHITE CELL COUNT	NO OF PATIENTS WITH POSITIVE X-RAY FINDINGS	AVERAGE DOSE PER 24 HOURS	AVERAGE DURATION OF TREATMENT	AVERAGE DURATION OF FEVER AFTER START OF TREATMENT	NO OF TREATMENT FAILURES
		yr	days	°F	$\times 10^3$		mg/kg of body weight	days	hr	
Aureomycin	11	4.2	4.2	104.4	19.7	11	61	5	20.2	0
Chloromycetin	18	3.2	3.6	104.0	21.2	18	124	5	23.0	0

after an uneventful hospital course. The child was still asymptomatic when seen in the clinic 1 week later. At this time, 13 days after the onset of illness, the cold-hemagglutinin and streptococcus MG titers were negative.

The hospital course is shown in Figure 3.

COMPARISON BETWEEN CHLOROMYCETIN AND AUREOMYCIN IN THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA

In view of the fact that the mode of management was essentially the same in cases of pneumococcal

out. The duration of therapy in both the aureomycin-treated and the chloromycetin-treated patients ranged between three and six days, with an average of five days.

After initiation of therapy with both chloromycetin and aureomycin, a rapid defervescence ensued. In the patients treated with aureomycin the temperature returned to normal within twelve to forty-eight hours, with an average of twenty and two-tenths hours, whereas in those treated with

chloromycetin, the duration of fever following institution of therapy ranged from twelve to sixty-four hours, with an average of twenty-three hours. This difference was not statistically significant. In regard to the rapidity of clearing of the nasopharyngeal culture of its pathogen, 61 per cent of the patients treated with aureomycin no longer showed pneumococci after five days and 70 per cent of those treated with chloromycetin were negative after a similar interval. In the aureomycin-treated group the time required for x-ray resolution ranged between four and seven days, with an average of five and nine-tenths days, whereas in the chloromycetin-treated series the range varied from three to twelve days, with an average of five and three-tenths days. In both groups the response to therapy was considered good in every patient and no failures were observed.

In view of the small number of cases treated in each group, only a few limited observations may be permitted from this comparative study. In the first place there did not seem to be any statistically significant difference in the response of patients with pneumococcal pneumonia to either aureomycin or chloromycetin since both drugs were extremely effective against this infection. No toxicity was observed when chloromycetin was employed except for a transitory leukopenia in several cases. On the other hand, the triad of nausea, vomiting and diarrhea was not infrequently encountered when aureomycin was used, and oc-

asionally the drug had to be discontinued in view of the persistence of gastrointestinal irritation. As for a comparison between either of these two new antibiotics with sulfonamides or penicillin in the treatment of pneumococcal pneumonia, no categorical statement is possible at the present time in view of the limited number of cases treated.

SUMMARY

Chloromycetin was used in the treatment of 33 cases of bacterial pneumonia in infants and children.

The therapeutic effect (based principally on the rapidity of return to normal of clinical, roentgenologic and laboratory findings) was considered favorable in all but 1 patient. In 32 of the 33 cases, the temperature was normal within three days of the initiation of the drug.

Chloromycetin may be regarded as an effective drug in the therapy of bacterial pneumonia.

We are indebted to Miss Sara Stevens, B.S., M.T., and Mrs. Susan Gouge for their technical assistance and to Miss Phyllis Allred, R.N., and Miss Lucie Knies, R.N., for their help in the compilation of statistics.

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RELIEF OF CHEST PAIN BY TETRAETHYLAMMONIUM CHLORIDE*

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PHILADELPHIA AND PHOENIXVILLE, PENNSYLVANIA

THE intravenous administration of tetraethylammonium chloride to a patient acutely ill with thrombophlebitis and pulmonary infarction unexpectedly relieved the patient's severe pleuritic pain. As a result of this observation, the effect of tetraethylammonium administration has been studied in other patients with chest pain.

The present report concerns observations made on 35 male and 5 female patients with chest pain due to infarction, trauma, pneumonia, pleuritis, tuberculosis, neoplasm, mediastinal emphysema or myocardial infarction.

Tetraethylammonium chloride was given intravenously, each cubic centimeter of solution containing 100 mg. of the drug. Syringe injection

RESULTS

In all cases a diminution of pain was noted. In some patients the effect was slight, being manifested chiefly by ability to breathe more deeply, in others the relief was considerable although brief in duration, but in the majority relief was marked and prolonged.

The results are summarized in Table 1. Included as having experienced marked relief are patients who were completely free of pain for at least an hour and a half or almost completely free for at least four hours, the majority of patients included in this group obtained relief for considerably longer periods, and in most cases the pain did not recur in its original intensity. The degree and duration of relief seemed to be influenced by the age of the patient as well as by the nature of the lesion responsible for the pain. Patients less than fifty years of age obtained satisfactory relief more often than older patients (Table 2), but relatively few older persons were treated because of reluctance to use this drug in patients with degenerative changes.

TABLE 1 *Effect of Tetraethylammonium Chloride on Chest Pain*

CAUSE OF PAIN	NO OF PATIENTS	SLIGHT OR MODERATE RELIEF	MARKED RELIEF
		NO OF CASES	NO OF CASES
Pulmonary infarction	8	2	6
Trauma	15	4	11
Pneumonia and pleuritis	8	4	4
Tuberculosis	5	4	1
Neoplasm	2	1	1
Mediastinal and cardiac disease	2	0	2
Totals	40	15	25

was made slowly, while the blood pressure was being measured in the other arm, administration was suspended if the diastolic blood pressure fell, and was resumed as the pressure rose. Only in older and in debilitated patients was there usually a marked fall in blood pressure.

Originally, an effort was made to give each patient 3 or 4 cc. of solution (300 to 400 mg.). These amounts were well tolerated by young patients with acute illnesses, but in others the fall in blood pressure often permitted injection of only 2 or 3 cc. More recently, a smaller dose of 3 mg. per kilogram of body weight has been employed. No severe reactions have been encountered, and in no case has it been necessary to use neostigmine for control of circulatory collapse. Patients were kept in a recumbent position for thirty minutes after administration of the tetraethylammonium chloride, to avoid symptoms due to postural hypotension.

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TABLE 2 *Effect of Tetraethylammonium Chloride on Chest Pain (Influence of Age)*

AGE	NO OF PATIENTS	SLIGHT OR MODERATE RELIEF	MARKED RELIEF
		NO OF CASES	NO OF CASES
30 or Under 50	31	10	21
50 and over	9	5	4

Application of the chi-square test failed to demonstrate a significant difference between the results in the two age groups, this may have been due in part to the small number of older patients, and additional studies will be required before definite conclusions concerning the effect of age can be drawn.

Pulmonary Infarction

Eight patients with severe pleuritic pain due to pulmonary infarction were treated. In 5, aged twenty-four to fifty-four years, with pain unrelieved by morphine, the response to tetraethylammonium chloride administration was prompt, complete and prolonged. In another patient, aged fifty-five years, the relief of pain was marked but incomplete, whereas 2 patients, aged sixty-four and sixty-six,

remained in continued pain and discomfort although local tenderness over the thorax was diminished, and it was evident that deeper respirations were possible

Traumatic Injuries

Four patients with pleuritic pain due to rib fractures were treated. Prompt and almost complete relief of pain for a six-hour period was obtained in an Army nurse, and similar relief of pain for an interval of five hours occurred in another woman with rib fractures incurred in an automobile accident. Two men, both alcoholic, experienced only slight and transient relief from tetraethylammonium chloride.

Striking results were noted in a group of 11 patients with severe pleuritic pain following diagnostic and therapeutic procedures. The pain followed aspiration biopsies of the liver in 8 patients, administration of 200-mg doses of tetraethylammonium chloride gave prompt and impressive relief in all but 1. Severe pleuritic pain following a thoracentesis was completely relieved in 1 patient. Complete relief was obtained with only 150 mg in a patient whose pleuritic pain developed after a therapeutic brachial-nerve block. Pleuritic pain occurring after a first-stage thoracoplasty in a patient with tuberculosis disappeared almost completely after a 300-mg dose, but returned to its original intensity in forty-five minutes.

Pneumonia and Pleuritis

Six patients with moderately severe pain due to pneumonia were given tetraethylammonium chloride. The relief was complete and prolonged in 2 but was only partial in the others. Two patients who had severe pleuritic pain without roentgenologically demonstrable cause, presumably cases of pleuritis, were treated. Prompt and complete disappearance of pain was obtained. One patient noted a return of slight pain in twelve hours, the other patient experienced no recurrence.

Tuberculosis

Five tuberculous patients who had chest pain only on deep inspiration and cough were treated. The results were striking only in 1, although in the others the pain on respiration and cough was diminished for an average interval of four hours.

Neoplasm

Complete relief of severe pleuritic pain for an hour and a half was obtained in a patient with rib involvement by multiple myeloma, but only slight relief occurred in a patient with metastatic sarcoma.

Mediastinal and Cardiac Disease

A young woman with severe precordial pain due to spontaneous mediastinal emphysema obtained

prompt, complete and permanent relief after administration of 125 mg of tetraethylammonium chloride. A forty-two-year-old man with acute myocardial infarction whose precordial pain remained agonizing after 25 mg ($3/8$ gr) of morphine subcutaneously and 15 mg ($1/4$ gr) intravenously obtained immediate and permanent relief after injection of 300 mg of tetraethylammonium chloride. Continuous electrocardiographic and careful clinical observation during and after administration of the drug revealed no untoward effects.

COMMENT

An action of tetraethylammonium chloride upon pleural and mediastinal pain apparently has not been previously reported. Lyons and his associates¹ noted dramatic relief of pain in 2 patients with acute myocardial infarction who were given tetraethylammonium chloride, but these investigators considered that the drug was contraindicated in the presence of coronary-artery disease. More recently, Shea and his co-workers² have reported the use of tetraethylammonium chloride for relief of cardiac pain in 16 patients with myocardial infarction or coronary insufficiency, and Christy³ has studied intramuscular administration of this drug for the treatment of angina pectoris.

The pharmacologic and physiologic implications of these observations are of considerable interest. The action of tetraethylammonium chloride is not that of a general analgesic, during its action thoracic skin sensitivity to painful stimuli is not diminished.

Tetraethylammonium chloride is known to exert appreciable psychic side effects, and a psychogenic influence cannot be excluded in the patients who appeared to obtain slight or even moderate relief of chest pain after its use. It is unlikely, however, that the complete relief occurring in patients severely ill with definite organic lesions can be considered psychogenic, especially since in many cases injections of morphine and procaine had previously been ineffectual. In fact, the action of tetraethylammonium chloride was most striking in patients who manifested the least psychologic and physiologic disturbance.

The mode of action of tetraethylammonium chloride in relieving chest pain is uncertain. Capps⁴ demonstrated that pain can be elicited by trauma to the parietal but not to the visceral pleura. The belief that pleural pain is due to irritation or inflammation of the parietal pleura and is carried through sensory fibers of the intercostal nerves has been questioned by Price,⁵ who pointed out that intercostal-nerve blocks with procaine relieved pleuritic pain for much longer intervals than were attributable to the anesthetic action of procaine. Bennett and Latham⁶ offered as an explanation the theory that the pain of pleurisy, like the pain of a sprained ankle, is due to muscle spasm, and postulated that a vicious circle was thereby initiated.

so that temporary interruption of the chain by the anesthetic action of procaine resulted in a prolonged relief. Their observation that intravenous calcium administration and curare were effective in alleviating pleuritic pain supported this theory. If pleural pain were the result of intercostal muscular spasm, the effect of tetraethylammonium chloride might be due to its curare-like activity, which however, is exerted not by a curarizing action at the myoneural junction of skeletal muscles, but by a blocking effect at the ganglionic synapse.⁷

In addition to an action on a hypothetical muscle spasm it is necessary, to explain the relief of cardiac pain, to postulate, as Shea et al.² have done, an action upon coronary-artery spasm. This does not appear to be an adequate explanation for the effect of tetraethylammonium chloride upon pain due to acute myocardial infarction, and the possibility should be considered that the relief of chest pain by tetraethylammonium chloride is the result of a direct action on sensory pathways, interrupting afferent flow either at nerve ending, at synapse or centrally. Evidence suggesting a direct action upon sensory pathways has recently been provided by the observation of Sonnenschein, Jenny and Pfeiffer⁸ that alterations in pain thresholds of the finger pads and nail beds are produced by administration of tetraethylammonium chloride.

The cardiovascular effects of tetraethylammonium chloride limit the application of the drug for relief of chest pain, especially in older patients. Tetraethylammonium chloride is a drug that must be used with caution in patients with hypertension or arteriosclerosis, and should not be used in patients with high diastolic pressures or impaired renal function. The alarming or fatal reactions reported have followed use of high dosages⁹ or rapid administration,¹⁰ although a profound reaction occurred in a young woman after injection of only 230 mg.¹¹ Serious reactions appear to be infrequent, however, when small doses are administered with care. Naide¹² has observed no severe reactions in the course of 1000 injections in ambulatory patients. He administered 200 mg or less in patients under fifty years of age, but determined the dosage in patients over the age of fifty by response to a test injection of 50 mg.

Use of tetraethylammonium chloride should afford little danger to hospital patients free of advanced renal or cardiovascular disease when used at the rate of 3 mg per kilogram of body weight. The value, especially in patients with pulmonary disease, of an analgesic agent that does not, like morphine, suppress cough and encourage atelectasis is evident. Tetraethylammonium chloride in low dosage provides a method of treatment worthy of trial in patients with severe chest pain not relieved by small doses of codeine or meperidine.

SUMMARY

Tetraethylammonium chloride administered intravenously in relatively small dosage has been observed to relieve chest pain due to a variety of conditions, including pulmonary embolism, trauma, pneumonia, pleuritis, tuberculosis, neoplasm, mediastinal emphysema and myocardial infarction. Relief was notably complete and prolonged in patients with pain due to infarction and trauma. These results appear to justify a further trial of tetraethylammonium chloride for the treatment of severe chest pain.

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THEPHORIN OINTMENT IN PRURITIC DERMATOSES

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SINCE the report of Fournau¹ and his French associates, there has been a widespread interest in the use of the so-called antihistaminics or histamine antagonists for diseases with an allergic background. Until quite recently, the antihistaminic drugs have been administered orally with good effect, especially in certain dermatoses such as the acute urticarias and urticarial drug reactions and some of the physical allergies.

The success achieved with the oral administration of the antihistaminic drugs in the allergic type of dermatoses led to their topical use in similar diseases. In 1947 Mayer² reported experimental evidence that the local application of 5 per cent triplennamine hydrochloride (Pyribenzamine) protected guinea pigs against epidermal sensitization to subsequent applications of paraphenyldiamine. Shortly thereafter, Feinberg and Bernstein³ used 2 per cent Pyribenzamine ointment in 33 cases of atopic dermatitis and stated that 24 of these patients noted consistent relief from the use of the ointment. At the same time, Sulzburger and his associates⁴ reported that the local use of Pyribenzamine cream was of

ment had good to excellent results in 55 per cent of his cases of atopic dermatitis, 75 per cent of lichen chronicus simplex and 60 per cent of miscellaneous pruritic dermatoses. Shelmire also noted a 13 per cent sensitization index in his series of cases and stated that Thephorin ointment was far superior to Pyribenzamine ointment in his experience.

In their series of cases, Laymon and Schmid found that Thephorin ointment had moderate to excellent results in 73.5 per cent of cases of circumscribed neurodermatitis. Their results in atopic dermatitis were as follows: excellent, 0; moderate, 55.5 per cent, and worse, 44.5 per cent. In their cases of miscellaneous pruritic dermatoses, they reported excellent results in 43 per cent and moderate improvement in 57 per cent of the cases.

PERSONAL EXPERIENCE WITH THEPHORIN OINTMENT

Because of the marked difference of opinion concerning the therapeutic value of the topical use of Thephorin ointment in so important a group of pruritic dermatoses, the study of the problem

TABLE 1 *Results of Treatment with Thephorin Ointment*

DIAGNOSIS	TOTAL No. OF CASES	INITIAL RESULTS			SUBSEQUENT RESULTS*		
		GOOD TO EXCELLENT	SLIGHT TO FAIR	NO EFFECT	PATIENT WORSE	REFRACTORY CONDITION	SENSITIZA- TION
Neurodermatitis disseminata	24	0	8 (33%)	10 (42%)	6 (25%)	6 (25%)	2 (8%)
Lichen chronicus simplex	26	10 (39%)	6 (23%)	10 (39%)	0	2 (8%)	0
Chronic dermatoses with pruritus	24	10 (42%)	2 (8%)	11 (50%)	0	4 (17%)	2 (8%)

*Improved patients.

distinct value only in lichen chronicus simplex and was of no value in atopic dermatitis.

In August, 1948, Woodridge and Joseph⁵ reported the local use of 2-methyl-9-phenyltetrahydro-1-pyridindene (Thephorin) in disseminated neurodermatitis. They used a 5 per cent ointment of Thephorin in a carbowax vehicle. Of 23 cases of neurodermatitis disseminata, Woodridge and Joseph stated that 9 (39 per cent) showed 75 per cent or more clearing and 8 (35 per cent) showed 50 per cent clearing. Thus, approximately 74 per cent of these patients were much improved with Thephorin. However, most of them also took Thephorin orally.

Later in 1948, Shelmire⁶ and Laymon and Schmid⁷ reported the use of Thephorin locally in pruritic dermatoses. Shelmire stated that Thephorin oint-

ment was undertaken. It was decided that, for a report of this nature to be of utmost value, the patients reported upon should be carefully followed over a period of months by the same observer. In this way, one could evaluate the results of the medication more exactly, and also determine whether any of the patients became resistant or sensitized to the topical remedy. All the patients were observed for a period before treatment with Thephorin ointment was instituted, to establish a definite diagnosis and to eliminate any cases that cleared up spontaneously.

In all, this report covers 74 cases. Of these, 24 were neurodermatitis disseminata, 26 were lichen chronicus simplex (neurodermatitis circumscripta) and 24 were miscellaneous dermatoses associated with pruritus. The group of neurodermatitis disseminata included typical cases of atopic dermatitis and allergic infantile eczema. The mis-

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cellaneous group of chronic dermatoses associated with pruritus included typical cases of so-called nummular eczema. The results of treatment are shown in Table I.

DISCUSSION

Most of the cases of neurodermatitis disseminata did poorly with Thephorin ointment. Six of the 8 patients in whom there had been an initial slight to fair improvement subsequently became refractory to the ointment, and 2 of these patients became sensitized. A good percentage of the patients definitely became worse with the use of Thephorin ointment.

Thirty-nine per cent of the patients with lichen chronicus simplex were very much improved. Two (8 per cent) of these became refractory on continued use of the ointment.

Approximately half the miscellaneous group of chronic dermatoses associated with pruritus were improved with Thephorin ointment. Four (17 per cent) of these improved cases became refractory to the ointment, and 2 patients (8 per cent) became definitely sensitized.

CONCLUSIONS

Thephorin ointment is of very little use in neurodermatitis disseminata.

Thephorin ointment is of real therapeutic value in lichen chronicus simplex (neurodermatitis circumscripta) and chronic dermatoses associated with pruritus.

About half the patients with initial improvement became refractory to continued use of the ointment.

Thephorin ointment has a sensitizing index of 16 per cent.

14 Maple Street

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THE USE OF WETTABLE DDT IN PEDICULOSIS

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MANY forms of therapy have been advocated for the control of the various types of infestation with pediculi. These have varied from the innocuous vinegar rinses to the more toxic derivatives of the benzene ring. Many of them are objectionable to the patient because of odor or difficulty of use. Not a few are severe skin sensitizers, and some are metabolic poisons.

With the advent of DDT, a new potent pediculicide was available and was used extensively as a powder by the armed forces. For the past two years, I have been using a "wetable DDT" in my practice with unprecedented success.

The wettable DDT that has been used is the type that is available through farm and seed stores and many gasoline stations. It is used by farmers, horticulturists, and others for the control of animal parasites of plant life. It is a fine, silky-smooth, white, fluffy powder, available in strength of 55 per cent active ingredient. When mixed with water, it forms, on agitation, a soapy emulsion that is very effective in the eradication of lice.

The patient is advised to wet the parts affected with water that is, the scalp hair in pediculosis

capitis, the pubic and axillary hair in pediculosis pubis and the clothing in pediculosis corporis — and then to make a lather with the wettable DDT powder. The lather is allowed to stay on the parts for fifteen minutes and then is washed out with water. One such treatment will kill all lice, but will not affect the nits or ova that contain unhatched lice. Since the remaining nits will hatch into live lice within two weeks,[†] it is necessary to repeat this fifteen-minute treatment once weekly for three weeks. The second weekly treatment will kill all the lice that have hatched from the first day to the seventh day and the third weekly treatment will kill all that have hatched from the seventh to the fourteenth day. Since it takes a louse eleven to thirteen days to mature, and since a louse less than eleven days old is unable to copulate and lay eggs,[‡] it is at once obvious that with this method of treatment, no nits will be laid down after the first treatment. Since nits hatch within fourteen days, it is evident that by the third treatment (the fourteenth day) all the eggs originally present will have hatched and no further lice will be produced from

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[†]Craig C. F. and Faust, E. C. *Clinical Parasitology*. Fourth edition. 871 pp. Philadelphia: Lea & Febiger, 1945.

them by the end of the fourteenth day (third day of treatment)

Itching is relieved immediately after the first treatment (unless there is a dermatitis, pyogenic infection or scabies complicating the picture)

No dermatitis has resulted from this exposure to DDT, nor have there been any toxic metabolic manifestations. It is a simple procedure and is especially time and labor saving.

The following, a simple, large-scale scheme, will eradicate all lice from institutions, such as orphanages and hospitals for the care of patients with chronic disease, that are plagued by such infestations. All persons in the institution (including not only the inmates but all the personnel of the institution that are affected) are treated once weekly for three weeks. All new patients are given the same treatment for the first three weeks of their hospitalization. This eradicates the infestation and prevents any new patient from bringing in the disease again.

If wettable DDT is not available, a satisfactory substitute is a paste of equal parts of 55 per cent regular DDT powder with one of the newer synthetic shampoos or detergents, such as Drene, Halo,

Vel and Phisoderm, or a powder from equal parts of regular DDT and Dreft, Swerl and so forth. This paste or powder is used in the same manner as the 55 per cent wettable powder.

Approximately, 15 gm (1 tablespoonful) of wettable powder will be sufficient for the average male scalp and about 60 gm (4 tablespoonfuls) for the average female scalp, 15 gm is sufficient for each treatment of pediculosis pubis, and about 120 gm for that of a tubful of clothing. In pediculosis corporis a single treatment of the clothing followed by ironing with a hot iron is sufficient to eradicate the disease.

It is important to treat all the infected members of the household at the same time.

SUMMARY

Wettable DDT powder (55 per cent) is an effective remedy for pediculosis.

Its use is simple, clean and economical.

A method of therapy is presented for the eradication of lice in large institutions as well as in individual cases.

520 Commonwealth Avenue

MEDICAL PROGRESS

HEMORRHAGIC DISEASES (Concluded)*

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CLOTTING TIME OF RECALCIFIED PLASMA — "RECALCIFICATION TIME"

Principle

If an optimal amount of calcium is added to oxalated plasma, containing an optimal number of platelets, coagulation results, and the time required for clotting has been termed the "recalcification time." Such a recalcification time depends on the concentrations of the various factors necessary for coagulation, including the blood platelet. In essence, it is a measurement of the coagulation time of plasma.

Method

A sample of 4.5 cc of venous blood is mixed with 0.5 cc of 0.1 molar solution of potassium oxalate.

*Adapted from *A Syllabus of Laboratory Examinations for Clinical Diagnosis* (in press) by permission of the Harvard University Press.

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The blood is centrifuged§ at 1000 rpm for five minutes, and the plasma removed. Then, 0.1 cc of this plasma is added to a 10 by 75 mm test tube without a lip, and the tube is placed in a water bath at 37.5° C. To the plasma is added 0.2 cc of 0.025-molar calcium chloride solution, a stop watch is started, and the contents are gently mixed. The tube is observed for coagulation at sixty seconds and every fifteen seconds thereafter, *the tube being kept in the water bath with as little agitation as possible*. The end point is complete coagulation of the plasma. The normal range of coagulation time with plasma centrifuged at 1000 rpm for five minutes is 90 to 120 seconds.^{79¶}

Limitations and Interpretations

In general it can be said that any condition associated with prolongation of coagulation of whole blood is also associated with prolongation of the clotting time of recalcified plasma. Such prolonga-

§The platelet content of plasma centrifuged under these conditions is 350 to 800 × 10³/mm³; an optimal number thus being insured when the platelet count of the whole blood is normal.

¶Note that the coagulation time of recalcified plasma is more rapid than that for whole blood; the mechanism of this is unknown.

tion is nonspecific and not indicative of any single disorder, and the interpretation of results is essentially the same as for the coagulation of whole blood. The primary point of difference between the coagulation time of recalcified plasma and the coagulation time of whole blood is the profound effect platelets have on the former and the slight effect on the latter when observed in glass tubes.

In severe *thrombocytopenia* the recalcification time is prolonged, such prolongation being directly proportional to the total number of blood platelets. The critical level of platelets at which prolongation occurs is about $100 \times 10^3/\text{mm}^3$ of plasma with the direct method of counting. This would correspond to a platelet count of 50 to $60 \times 10^3/\text{mm}^3$ of whole blood*. Thus, it is evident that the platelet count must be rather severely depressed before an alteration in recalcification time occurs. Prolongation of the recalcification time is also seen in hemophilia, *parahemophilia* (lack of "Factor V")¹² and *afibrinogenemia*. In *scurvy* and *thrombasthenia* the recalcification time is normal. Thus, it becomes evident that prolongation of the recalcification time may result from a deficiency of platelets and a deficiency of one or more of the factors of plasma necessary for coagulation.

SCREENING TESTS FOR ABNORMAL COAGULATION OF BLOOD

Principle

When mixtures are made of whole unaltered venous blood from a patient and from a normal subject, the coagulation time may be used as a screening test to detect abnormalities of the clotting mechanism. For example, in coagulation defects resulting from a *deficiency of a plasma factor*, the addition of normal blood may restore the coagulation time toward normal. This may occur in conditions such as hemophilia, afibrinogenemia and deficiency of "prothrombin accelerator" substances. Conversely, in cases of *circulating anticoagulant*, the addition of the patient's blood to that of the normal subject will prolong the coagulation time of the normal blood, as in heparinemia and other conditions with circulating anticoagulants of undetermined nature.

Technically, mixtures may be made of samples of whole unaltered blood or of oxalated plasma with subsequent recalcification of the plasma. Because of the convenience of handling oxalated plasma, it is more frequently used.

Methods

Mixtures of whole blood. Two 10-cc sterile syringes and needles are rinsed with sterile saline solution, and 3 cc of sterile saline solution is then placed in each syringe. Simultaneous venipunc-

tures are performed on the patient suspected of abnormal coagulation and on a normal subject. The saline solution† is then injected at the same time and same rate into each subject. A stop watch is started, and 10 cc of venous blood is withdrawn from each subject at the same rate. Mixtures are then made of the blood of the patient and that of the normal subject by gentle transfer of samples to six saline-rinsed culture tubes without lips (13 by 100 mm) in the amounts shown in Table 2.

In this system the coagulation times are determined for the whole bloods of both subjects as well as for mixtures.

Mixtures of oxalated plasma. Reagents Potassium oxalate is used as an anticoagulant. One makes a

TABLE 2 Preparation of Mixtures of Whole, Unaltered Venous Blood from a Patient with Hemorrhagic Disease and a Normal Subject for Observation of Plasma Defects or Anticoagulant Activity on the Clotting Time

SOURCE OF BLOOD	VOLUME OF BLOOD IN TUBE					
	TUBE NO 1	TUBE NO 2	TUBE NO 3	TUBE NO 4	TUBE NO 5	TUBE NO 6
	cc	cc	cc	cc	cc	cc
Patient	2.0	1.6	1.2	0.8	0.4	0.0
Normal subject	0.0	0.4	0.8	1.2	1.6	2.0

0.1-molar solution by dissolving 18.423 gm of crystalline potassium oxalate ($\text{K}_2\text{C}_2\text{O}_4 \cdot \text{H}_2\text{O}$) in 1000 cc of distilled water. Then 1.0 cc of this solution is used to prevent coagulation of 9.0 cc of whole blood.

Calcium chloride. 0.025-molar solution, is made by dissolving of 2.77 gm of calcium chloride (purified anhydrous) in 1000 cc of distilled water.

Technic. A sample of 4.5 cc of venous blood is obtained‡ from the patient and an equal sample

TABLE 3 Preparation of Mixtures of Oxalated Plasma from Patient and Normal Subject for Observation of Plasma Defects or Anticoagulant Activity on the Clotting Time

SOURCE OF PLASMA	VOLUME OF PLASMA IN TUBE					
	TUBE NO 1	TUBE NO 2	TUBE NO 3	TUBE NO 4	TUBE NO 5	TUBE NO 6
	cc	cc	cc	cc	cc	cc
Patient	0.2	0.4	0.1	0.1	0.1	0.0
Normal subject	0.0	0.1	0.1	0.2	0.4	0.2

from a normal subject, each sample is accurately added to 0.5 cc of 0.1-molar solution of potassium oxalate and thoroughly mixed. The plasma is obtained by centrifugation of the oxalated whole blood at 1000 rpm for five minutes. Centrifugation is done simultaneously in the same centrifuge, thus ensuring the same speed of centrifugation for an

*When blood is centrifuged at 1000 rpm for five minutes the platelets are concentrated in the plasma layer being separated from the red cells.¹¹

†This step permits each operator to synchronize his obtaining of a blood sample and serves to decrease contamination of blood by tissue juice.

‡There is no need to perform venipunctures simultaneously and blood samples can be handled without hurry.

identical period for the two plasmas. The plasmas are mixed in a series of six dry culture tubes without lips (10 by 75 mm) in the amounts shown in Table 3, and the contents of each tube is mixed by inversion. Then 0.1-cc samples of each tube are transferred to separate dry culture tubes without lips (10 by 75 mm) and the tubes are placed in a water bath at 37.5°C. The coagulation times of recalcified mixtures of plasma and of each subject's plasma are then determined in duplicate, as described above, by the addition of 0.2 cc of 0.025-molar solution of calcium chloride.

Limitations and Interpretations

The technical limitations of these procedures are identical to those for the determination of the coagulation time. It is important to execute an immediately successful venipuncture on each subject so as to reduce to a minimum contamination of the blood with tissue juice. By the injection of 3 cc of sterile saline solution contamination is further reduced. A small amount of tissue juice will grossly accelerate blood coagulation and obscure mild plasma defects or mild anticoagulant activity. When mixtures of oxalated plasma are used as a screening test for abnormal coagulation it is essential that the speed and duration of centrifugation be identical for both samples, since marked reduction in the number of platelets will result in prolongation of the coagulation time of recalcified plasma.

In any condition in which there is a deficiency of one or more of the plasma components necessary for proper coagulation there is prolongation of the coagulation time. By addition of plasma factors to the abnormal blood, in the form of unaltered whole blood or plasma, the coagulation time of the abnormal blood is reduced toward normal. Thus, in such conditions as *hemophilia*, *fibrinogenopenia*, *afibrinogenemia*, *severe hypoprothrombinemia* and *parahemophilia*, the procedures outlined above will give normal coagulation times in all tubes except No. 1, in which the coagulation time will be variously prolonged depending on the severity of the plasma defect. In cases of deficiency of plasma factors the coagulation time of mixtures of whole blood or of mixtures of recalcified plasma will *not* be prolonged. Once a plasma defect is discovered, it becomes necessary to determine its nature more specifically; detailed methods are described by Owren.¹⁹

Abnormal coagulation as the result of *anticoagulant activity*, however, characteristically results in prolongation of the coagulation time of mixtures of whole blood and of recalcified plasma (prolonged in tubes No. 1 to 5 in Table 2 and 3). As the concentration of abnormal blood or of plasma is increased in the mixtures greater prolongation of the coagulation time results. Once such anticoagulant activity is demonstrated, an attempt must be made to determine the type of anticoagulant that is present. This is done by diagnostic

procedures involving the use of special reagents that are, as a rule, only available for research purposes. Therefore, reference should be made to the methods for determination of *antithrombin* and *antithromboplastin* as outlined by Quick.¹ *Hyperheparinemia* as a cause of abnormal coagulation has recently been shown to occur with *ionizing radiation*¹¹ in *leukemia*¹² and in certain cases of *thrombocytopenia*.¹² The method of determining the degree of hyperheparinemia consists in adding a natural antiheparin (protamine sulfate) in increasing amounts to accurately heparinized venous blood and determining the amount of protamine required to reduce the coagulation time of the heparinized blood to normal. A normal control is always used for comparison (Allen et al.¹³).

By determination of the coagulation time of mixtures of whole blood or oxalated plasma, it is thus possible to differentiate plasma defects from circulating anticoagulants as cause of abnormal coagulation. Once such a distinction has been made it is necessary to carry out special procedures for the more specific identification of the defect or anticoagulant.

DETERMINATION OF PROTHROMBIN ACTIVITY

Principle

When optimal amounts of thromboplastin and calcium are added to citrated plasma, the factor measured is the speed of conversion of prothrombin to thrombin if other abnormalities* can be excluded. The time required for this conversion has been measured quantitatively as an arbitrary and biologic test in which the clotting time of the plasma becomes a measurement of its prothrombin activity. Measurement of prothrombin activity of plasma has become an important laboratory examination because it has important diagnostic and prognostic significance in diseases of the liver and in hemorrhagic diatheses and because the use of Dicumarol in the treatment of thromboembolic disease requires careful control of the prothrombin level, since death may occur from hemorrhage due to extreme hypoprothrombinemia.

Accordingly, the method of determining prothrombin activity in terms of its concentration in percentage of normal is of importance. The method of Quick¹ is a standard one-stage procedure and is described below in detail. Many modifications of this technic have evolved. One such modification, using dilution of the plasma with prothrombin-free plasma,³⁵ is known to give a high degree of accuracy and is also described below. The more complete two-stage method³⁶ is too demanding for clinical purposes; in essence, this method measures quantitatively the amount of thrombin formed from prothrombin.

*Rarely there may be fibrinogenopenia or afibrinogenemia, deficiency of prothrombin accelerators or a circulating anticoagulant.

Quick Method

Reagents A 0.1-molar solution of sodium citrate is used as an anticoagulant. It is made by dissolving of 29.412 gm of sodium citrate ($\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2 \text{H}_2\text{O}$) in 1000 cc of distilled water, 10 cc of this solution is used to prevent coagulation of 90 cc of whole blood.

Thromboplastin is prepared by the addition of 4 cc of a sterile solution of sodium chloride (0.85 gm per 100 cc) and 0.05 cc of a solution of sodium oxalate (1.34 gm per 100 cc) to one ampoule (0.15 gm) of lyophilized rabbit brain (Difco) that has been extracted with acetone. This mixture is incubated at 48°C for ten minutes, with agitation every three minutes. Large particles of rabbit brain are then removed from the mixture by "filtration" through cotton: a small piece of cotton is loosely placed over the tip of a 20-cc volumetric pipette, the cotton-covered tip of the pipette being immersed in the emulsion and gentle suction applied. One should not centrifuge or filter through paper.*

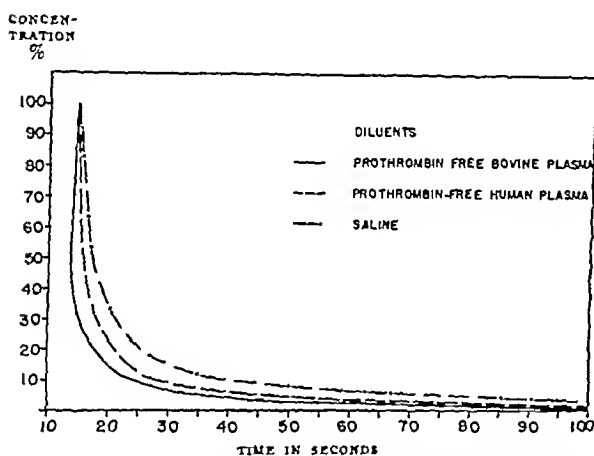


FIGURE 1 Effect of Three Different Diluents of Normal Human Plasma on the Prothrombin Time in Seconds¹⁸ (The Method of Rosenfield and Tuft⁵⁸ as Modified by Alexander and deFries,⁴⁰ Uses Prothrombin-Free Human as a Diluent, Frommeyer¹⁸ Uses Prothrombin-Free Bovine Plasma)

When used as a chart for the conversion of prothrombin time (seconds) to prothrombin concentration (per cent), the activity of the thromboplastin must be determined by replotting of the curve whenever the thromboplastin is changed.

Thromboplastin as thus prepared is quite stable for many weeks if kept frozen (-20°C) in 0.1-cc aliquots in standard culture tubes (10 by 75 mm) until ready for use. The potency of the thromboplastin is an essential element of the procedure and is standardized for each aliquot of material, as described below.

Calcium chloride, 0.025-molar solution, is made as described above under screening tests for abnormal coagulation.

Technic All tubes and reagents are maintained at 37.5°C in a water bath. To 0.1 cc of thrombo-

plastin solution in a standard culture tube with lip (10 by 75 mm) 0.1 cc of citrated plasma is accurately added. The tube is gently shaken to ensure mixing. With stop watch in hand, exactly 0.1 cc of calcium chloride (0.025-molar) solution is added, and at the same instant the stop watch is started. The tube is held in the water bath, and the contents are gently mixed. A few seconds before clotting is anticipated, the tube is removed from the water bath, held in a horizontal position and moved gently back and forth. Clotting of the plasma is the end point, it is taken as occurring at the instant at which the plasma is no longer completely fluid. This procedure is repeated as a check, and the second determination should agree with the first within half a second to one second to be considered accurate. The prothrombin time is recorded in terms of seconds. With knowledge of the prothrombin time, it is possible, by means of a prothrombin-time-concentration curve (Fig. 1), to determine the value in terms of percentage of normal.

Determination of Prothrombin by Means of Dilution with Prothrombin-Free Plasma

The problems in determining prothrombin by the Quick method may be largely resolved by the use of a modification⁴⁰ of the method of Rosenfield and Tuft⁵⁸.

Principle The principles of the method are as follows: the prothrombin time is determined on a sample of citrated plasma by the usual method of Quick to estimate the activity of the sample, and the citrated plasma is then diluted with prothrombin-free normal plasma. Dilution with prothrombin-free plasma is necessary if the prothrombin time is relatively short, corresponding to a prothrombin concentration of 30 per cent or more. It is immediately apparent from inspection of Figure 1 that a difference of a few seconds in prothrombin time in this range of the curve is equivalent to large differences in the concentration of prothrombin. For example, in Figure 2 a prothrombin time of fourteen seconds corresponds to 30 per cent prothrombin, whereas thirteen seconds corresponds to an apparent concentration of 45 to 100 per cent. Manifestly, there are two technical limitations of this method that make it unsound: the concentration cannot be read accurately on the steep part of the curve, and small errors of estimating the end point may be greatly magnified when the time in seconds is converted to concentration. To remove these limitations, the plasma is diluted so that the prothrombin concentration of the mixture will be approximately 10 per cent of normal, as shown in Figure 2, thus permitting observation of the prothrombin time in part of the curve in which the deviation of a few seconds produces insignificant changes in apparent prothrombin concentration. *Dilution with saline solution cannot be recommended since all clotting factors are thereby diluted.*

*The thromboplastin solution is a milky-appearing emulsion. Removal of the small particulate matter will remove most of the thromboplastin activity.

Reagents Thromboplastin and calcium chloride solution are prepared as described above. Potassium oxalate is used as an anticoagulant since oxalated plasma can be depleted of its prothrombin, whereas citrated plasma cannot. A 0.1-molar solution of potassium oxalate is made as described above under screening tests for abnormal coagulation, 10 cc of this solution is used to prevent coagulation of 90 cc of whole blood.

Adsorption of prothrombin Prothrombin is readily adsorbed by the addition for each 10 cc of oxalated plasma, of 100 mg of powdered barium sulfate. The mixture is shaken, incubated for ten minutes at 37.5°C with agitation every three minutes, and centrifuged at 3000 rpm for thirty minutes, the supernatant is poured off and put in the refrigerator at 4°C until ready for use. The prothrombin-free plasma should be used within 2 hours of its preparation and kept in the refrigerator during this period. This disadvantage can be overcome by lyophilizing of large quantities of prothrombin-free normal plasma and reconstitution of this plasma with buffered distilled water immediately prior to use.⁴⁸ According to Owren¹⁹ 50 per cent of "Factor V" is also removed by the barium sulfate adsorption of prothrombin although the amount used is not stated. This can be obviated by the use of prothrombin-free ox plasma as the diluent, since it is rich in "prothrombin accelerators."

Preparation of time-concentration curve In each laboratory a curve, such as that shown in Figure 1, must be prepared to determine the activity of the available thromboplastin for the conversion of prothrombin time to prothrombin concentration in percentage. The time-concentration curve is derived with prothrombin-free plasma, rather than physiologic saline solution, as the diluent of fresh normal plasma. The principle of the method is to collect and pool equal quantities of plasma from at least 5 to 10 normal subjects (preferably young males), 1 part of 0.1-molar solution of potassium oxalate being used for 9 parts of venous blood. A portion of the pooled plasma is treated with barium sulfate to remove prothrombin. With this prothrombin-free plasma as a diluent, the fresh pooled plasma is diluted serially to known concentrations of fresh plasma and the prothrombin time of each dilution determined as described below. From the known concentrations and times, a conversion curve is plotted as in Figure 1.

Technic of measuring prothrombin with prothrombin-free plasma A sample of 4.5 cc of venous blood is withdrawn and mixed with 0.5 cc of 0.1-molar solution of sodium citrate. This blood is centrifuged and the plasma removed. The prothrombin time of the undiluted sample of plasma is determined, the method of Quick, as outlined above being employed as the first step. If the prothrombin time is so short as to represent a prothrombin concentration of 20 to 30 per cent or more the prothrombin concen-

tration cannot be read accurately enough from the curve for proper reporting. The plasma is then diluted as described below.

As a second step, the plasma is diluted with prothrombin-free normal plasma so that the prothrombin concentration will be approximately 10 per cent of normal. The prothrombin time is then determined for the diluted sample, and the corresponding concentration in per cent is read from the curve, the

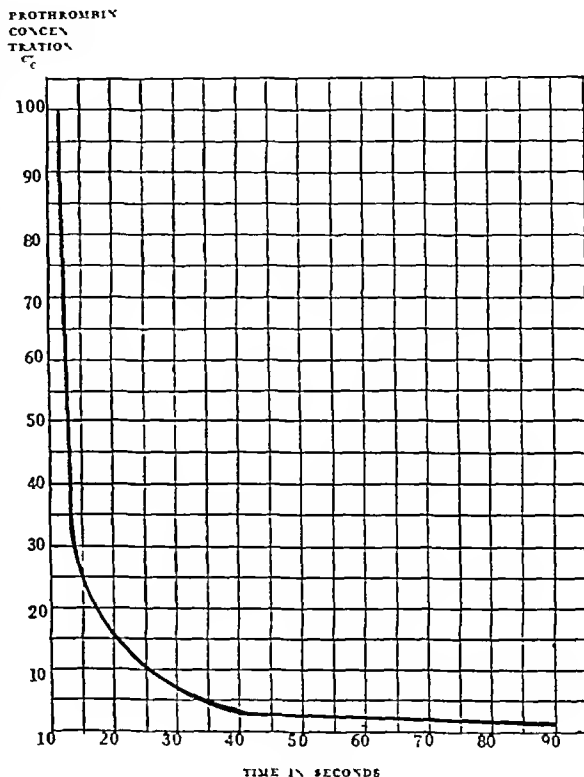


FIGURE 2 Chart for Conversion of Prothrombin Time (seconds) to Prothrombin Concentration (Per Cent)

The curve is made by dilution of a pool of fresh normal plasmas, prothrombin-free normal plasma being used as a diluent. This is the method of Rosenfield and Tuft,³⁰ as modified by Alexander and deLies.⁴⁰ The curve will vary with the activity of the thromboplastin and must be remade when the thromboplastin is changed.

concentration is then multiplied by the dilution factor and reported in terms of percentage.

As an example the prothrombin time of an undiluted sample of plasma is 13 seconds, corresponding to concentrations of prothrombin of from 40 to 100 per cent. The plasma is diluted, — 1 part of fresh citrated plasma with 9 parts of prothrombin-free plasma, — and the prothrombin time determined. If the time is twenty-eight seconds, this corresponds on the curve to a prothrombin concentration of 10 per cent, this is multiplied by 10 to correct for dilution, giving a final value of 100 per cent for the concentration of prothrombin.

Limitations and Interpretations

Many of the time-concentration curves for prothrombin that are reported in the literature have been prepared from *saline* dilutions of plasma. Such dilutions diminish the amount of other factors necessary for coagulation and will show erroneously delayed prothrombin times, which may not be reliable or accurate in the determination of prothrombin concentrations in the range of 30 to 100 per cent of normal. If prothrombin-free plasma is used as a diluent, as described above, more reproducible time-concentration relations are obtained since all elements essential for coagulation have been preserved, with the possible exception of a part of the "prothrombin accelerators" mentioned above.^{19, 46, 51, 55} This difficulty can be obviated by the use of lyophilized prothrombin-free ox plasma, which contains an excess of all these substances. The determination of prothrombin on plasma diluted to a 10 per cent concentration with prothrombin-free ox plasma permits a new order of *reproducibility* and *accuracy* and makes obsolete methods that attempt to interpret differences of one or two seconds that are equivalent to 50 per cent difference in prothrombin concentration.⁵⁸

The use of *Dicoumarol* to prevent the complications of thromboembolic phenomena has required a wide clinical application of the determination of prothrombin concentration. *Dicoumarol* presumably prevents the formation of prothrombin by the liver. Excessive administration produces a severe hypoprothrombinemia and a hemorrhagic tendency. The dosage is controlled by observation of the prothrombin time. Usually, it has been considered necessary to keep the prothrombin time approximately thirty to forty seconds, or the concentration between 4 and 8 per cent of normal, to prevent thrombotic phenomena.

The prothrombin determination is of value in detecting the absence of prothrombin as a cause of hemorrhagic diathesis and in the study of response to vitamin K therapy.

In diagnosis the interpretation of the prothrombin time requires a knowledge of factors other than prothrombin deficiency that may cause prolongation, and a knowledge of the sources of error in the test. A prolonged prothrombin time by Quick's method is found in *afibrinogenemia* even though the prothrombin concentration may be entirely normal as determined by the dilution method using prothrombin-free plasma as a diluent. In addition, deficiencies of "prothrombin accelerators" result in prolongation of prothrombin time unless the dilution method using prothrombin-free plasma is employed. The prothrombin concentration is usually normal in the other hemorrhagic diseases as shown in Table 1.

PROTHROMBIN CONSUMPTION

Principle

When unaltered normal venous blood is placed in a test tube, as in the determination of the coagulation time, clotting will normally occur within six to twelve minutes. When the clot is allowed to remain undisturbed for one hour after initial coagulation so as to ensure maximum coagulation, serum is expressed. The serum contains variable amounts of prothrombin, calcium, thrombin and serum "prothrombin accelerators," but *no fibrinogen*. Within two or three hours the thrombin present is converted to an inactive form, metathrombin. Various intervals are required for inactivation of the serum "prothrombin accelerators," but it appears likely from the available data that essentially complete inactivation occurs within twelve hours at a temperature of 37.5°C.^{19, 60, 64} Such serum will then contain prothrombin and calcium. If this serum is added to a mixture of thromboplastin, fibrinogen and calcium, clotting will usually occur. The time required for clotting of this mixture becomes a function of the prothrombin that was not used (consumed) in the formation of the clot and that remains in the serum. Apparently, the prothrombin is the major variable in such a reaction mixture, and thus a prothrombin time and prothrombin concentration are obtained from the clotting time. The difference between the original plasma concentration time and the residual serum concentration of prothrombin is termed the "prothrombin consumption." The technic of the test is that used by Quick,⁶⁵ with the exception that prothrombin-free human plasma is used as a source of fibrinogen rather than prothrombin-free rabbit plasma.

Modified Quick Method for Prothrombin Consumption

Reagents Thromboplastin and calcium chloride solution and prothrombin-free human plasma are prepared as described above.

Technic Venous blood is allowed to coagulate according to the method described above. The clotting time is noted. One hour after initial coagulation the tubes are centrifuged at 800 rpm for five minutes, the serum is removed and kept at 37.5°C for twenty-four hours.* A "prothrombin time" is determined as follows: to a mixture of exactly 0.1 cc of thromboplastin, 0.1 cc of prothrombin-free human plasma and 0.1 cc of 0.025-molar solution of calcium chloride is quickly added 0.1 cc of the unknown serum. A stop watch is started immediately upon addition of the serum to the mixture. The contents of the tube are shaken gently, and the instant the mixture is no longer *completely* fluid is taken as the end point. The prothrombin concentration can then be determined from the prothrom-

*Although serum is bacteriostatic a sterile technic may be employed without increasing greatly the difficulty of the procedure.

bin time in seconds, as outlined above. This procedure is done at one, three and twenty-four hours after coagulation.

Limitations and Interpretations

The limitations of a one-stage method for measuring prothrombin time are the same as those described above. However, the difference in prothrombin consumption between the normal and abnormal is so large that these technical limitations are of secondary importance. The method for determination of prothrombin concentration described by Rosenfield and Tuft⁵⁸ may be used, however, if desired. Biologic limitations exist, in that serum contains active "prothrombin accelerators" that govern the speed of the coagulation reaction and therefore the prothrombin time. There still remains considerable doubt concerning exactly when these "accelerators" become inactivated in serum that is stored at 37.5°C. From the available literature^{19, 60} the impression is gained that such inactivation is relatively rapid, there being little evidence of "prothrombin-accelerator" activity at the end of three hours of storage at room or water-bath (37.5°C) temperatures. On the other hand, one investigator⁶¹ reports 80 to 83 per cent activity after four hours of storage at 37.5°C. Because of the presence of active serum "prothrombin accelerators" as well as thrombin in the serum at one and three hours after coagulation, determinations of prothrombin concentration at these times are very difficult to evaluate. After a storage interval of twelve hours at 37°C, however, it is quite likely that the serum "prothrombin accelerators" are completely inactivated. By the use of prothrombin-free human plasma as a source of fibrinogen in the procedure, it is possible to maintain a relatively constant amount of available "prothrombin accelerators" in each reaction mixture after twelve hours of incubation of the serum.

By the procedure described, normal serum is found to have a residual prothrombin concentration of 10 to 20 per cent (80 to 90 per cent prothrombin consumption).

In *hemophilia* the serum has a prothrombin concentration of 80 to 100 per cent, and hence a low prothrombin consumption (0 to 20 per cent). Such a finding confirms the theory that in hemophilia prolonged coagulation is the result of improper formation of thrombin from prothrombin. That hemophilic blood ultimately coagulates is explained⁶² on the basis that a small amount of prothrombin is eventually converted to thrombin over a prolonged period. Since thrombin is enzymatic in action, even a small amount is capable of converting fibrinogen to fibrin and thus resulting in superficial clotting as arbitrarily measured in glass tubes. The small amount of thrombin so formed will then slowly and continuously convert fibrinogen to fibrin until no fibrinogen remains in the

serum. On the other hand, the total conversion of prothrombin to thrombin depends largely on the amount of active plasma thromboplastin and "prothrombin accelerators" present, the reaction between thromboplastin and prothrombin being, most likely, stoichiometric.⁵⁰ Thus, the lower the plasma thromboplastin concentration the smaller the amount of prothrombin that will be consumed or converted to thrombin in the process of coagulation. In *hemophilia* the plasma thromboplastin concentration is considered to be extremely low, whereas the "prothrombin accelerator" concentration is normal.¹⁹

In *thrombocytopenia* the prothrombin consumption is approximately 40 to 60 per cent.^{64, 66} The mechanism for reduced prothrombin consumption may result from a reduction in a "platelet enzyme," as described above. This enzyme is considered necessary for activation of a precursor (thromboplastinogen) of plasma thromboplastin. Plasma thromboplastin, as mentioned above, converts prothrombin to thrombin stoichiometrically. As a result of decreased numbers of platelets or alteration in platelet function or both, only a small amount of active plasma thromboplastin is formed.

Prothrombin consumption is normal in *afibrinogenemia*, which indicates normal production of thrombin. The lack of coagulation in this disease is due to complete absence of fibrinogen, which thrombin would normally convert to fibrin, and is not concerned with any abnormality of prothrombin conversion.

In *parahemophilia* the conversion of prothrombin to thrombin has been shown to be slow owing to absence of an "accelerator substance." The total amount of prothrombin consumed in the process of clot formation, apparently, is of the degree of that seen in thrombocytopenia.¹⁹ This is explained on the basis that the "prothrombin accelerators" may be concerned primarily with the speed of conversion of prothrombin to thrombin and are therefore indirectly concerned with the total amount of prothrombin converted or consumed in a given period. Prothrombin consumption is normal in the remainder of the hemorrhagic diseases, as shown in Table 1. In the hemorrhagic diseases resulting from circulating anticoagulants and in thrombasthenia prothrombin consumption has not been reported.

It is evident, therefore, that the degree of prothrombin consumption depends on the presence of adequate amounts of plasma thromboplastin, platelet enzyme and "prothrombin accelerators."

DETERMINATION OF FIBRINOLYSIS

Normally, human plasma contains a balanced enzyme system consisting of the inactive precursor of a proteolytic enzyme, designated as profibrinolysin or plasminogen, and an antiproteolytic substance, designated as antifibrinolysin or antiplasmin. Under certain circumstances, the proenzyme be-

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The prothrombin determination is of value in detecting the absence of prothrombin as a cause of hemorrhagic diathesis and in the study of response to vitamin K therapy.

In diagnosis the interpretation of the prothrombin time requires a knowledge of factors other than prothrombin deficiency that may cause prolongation, and a knowledge of the sources of error in the test. A prolonged prothrombin time by Quick's method is found in *afibrinogenemia* even though the prothrombin concentration may be entirely normal as determined by the dilution method using prothrombin-free plasma as a diluent. In addition, deficiencies of "prothrombin accelerators" result in prolongation of prothrombin time unless the dilution method using prothrombin-free plasma is employed. The prothrombin concentration is usually normal in the other hemorrhagic diseases as shown in Table 1.

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Modified Quick Method for Prothrombin Consumption

Reagents Thromboplastin and calcium chloride solution and prothrombin-free human plasma are prepared as described above.

Technic Venous blood is allowed to coagulate according to the method described above. The clotting time is noted. One hour after initial coagulation the tubes are centrifuged at 800 rpm for five minutes, the serum is removed and kept at 37.5°C for twenty-four hours.* A "prothrombin time" is determined as follows: to a mixture of exactly 0.1 cc of thromboplastin, 0.1 cc of prothrombin-free human plasma and 0.1 cc of 0.025-molar solution of calcium chloride is quickly added 0.1 cc of the unknown serum. A stop watch is started immediately upon addition of the serum to the mixture. The contents of the tube are shaken gently, and the instant the mixture is no longer *completely* fluid is taken as the end point. The prothrombin concentration can then be determined from the prothrom-

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By the procedure described, normal serum is found to have a residual prothrombin concentration of 10 to 20 per cent (80 to 90 per cent prothrombin consumption).

In *hemophilia* the serum has a prothrombin concentration of 80 to 100 per cent, and hence a low prothrombin consumption (0 to 20 per cent). Such a finding confirms the theory that in hemophilia prolonged coagulation is the result of improper formation of thrombin from prothrombin. That hemophilic blood ultimately coagulates is explained⁶⁵ on the basis that a small amount of prothrombin is eventually converted to thrombin over a prolonged period. Since thrombin is enzymatic in action even a small amount is capable of converting fibrinogen to fibrin and thus resulting in superficial clotting as arbitrarily measured in glass tubes. The small amount of thrombin so formed will then slowly and continuously convert fibrinogen to fibrin until no fibrinogen remains in the

serum. On the other hand, the total conversion of prothrombin to thrombin depends largely on the amount of active plasma thromboplastin and "prothrombin accelerators" present, the reaction between thromboplastin and prothrombin being, most likely, stoichiometric.⁵⁰ Thus, the lower the plasma thromboplastin concentration the smaller the amount of prothrombin that will be consumed or converted to thrombin in the process of coagulation. In *hemophilia* the plasma thromboplastin concentration is considered to be extremely low, whereas the "prothrombin accelerator" concentration is normal.¹⁹

In *thrombocytopenia* the prothrombin consumption is approximately 40 to 60 per cent.^{64, 66} The mechanism for reduced prothrombin consumption may result from a reduction in a "platelet enzyme," as described above. This enzyme is considered necessary for activation of a precursor (thromboplastinogen) of plasma thromboplastin. Plasma thromboplastin, as mentioned above, converts prothrombin to thrombin stoichiometrically. As a result of decreased numbers of platelets or alteration in platelet function or both, only a small amount of active plasma thromboplastin is formed.

Prothrombin consumption is normal in *afibrinogenemia*, which indicates normal production of thrombin. The lack of coagulation in this disease is due to complete absence of fibrinogen, which thrombin would normally convert to fibrin, and is not concerned with any abnormality of prothrombin conversion.

In *parahemophilia* the conversion of prothrombin to thrombin has been shown to be slow owing to absence of an "accelerator substance." The total amount of prothrombin consumed in the process of clot formation, apparently, is of the degree of that seen in thrombocytopenia.¹⁹ This is explained on the basis that the "prothrombin accelerators" may be concerned primarily with the *speed* of conversion of prothrombin to thrombin and are therefore indirectly concerned with the *total amount* of prothrombin converted or consumed in a given period. Prothrombin consumption is normal in the remainder of the hemorrhagic diseases, as shown in Table 1. In the hemorrhagic diseases resulting from *circulating anticoagulants* and in *thrombasthenia* prothrombin consumption has not been reported.

It is evident, therefore, that the degree of prothrombin consumption depends on the presence of adequate amounts of plasma thromboplastin, platelet enzyme and "prothrombin accelerators."

DETERMINATION OF FIBRINOLYSIS

Normally, human plasma contains a balanced enzyme system consisting of the inactive precursor of a proteolytic enzyme, designated as profibrinolysin or plasminogen, and an antiproteolytic substance, designated as antifibrinolysin or antiplasmin. Under certain circumstances, the proenzyme be-

comes activated, resulting in the elaboration of the proteolytic enzyme, fibrinolysin or plasmin. The active enzyme received the name fibrinolysin from Dastre,⁸⁰ who found it to "destroy fibrin." Subsequent investigation has shown fibrinolysin to digest not only fibrin but also fibrinogen,⁸¹ prothrombin⁸² and, at least in one instance, a "prothrombin accelerator."⁸³ Because of the widespread alteration that can occur in the circulating blood and in clot formation, it becomes important to ascertain the presence or absence of this proteolytic enzyme as a cause of hemorrhagic diathesis. Since fibrinolysin (plasmin) is capable of digesting both fibrinogen and fibrin, it is evident that this enzyme can alter coagulation in any one of the following ways, depending upon its concentration: coagulation may be normal with subsequent *partial lysis* of the clot, coagulation may be normal with subsequent *complete lysis* of the clot, and there may be *no coagulation* because of rapid fibrinogenolysis and resultant afibrinogenemia.

Fibrinolytic activity is measured by observation of the stability of a clot of whole blood or of recalcified plasma. Further details are given in the excellent review by Macfarlane and Biggs.⁶⁷

Method

Whole-blood technic With sterile technic blood is obtained for determination of the coagulation time as outlined above, and the coagulation time is recorded. *It is important to watch closely for coagulation because fibrinolysis may be of such activity as to give the impression of incoagulability of the blood.* After coagulation has occurred the sample is maintained at 37.5°C in a water bath and observed for dissolution of the clot at half an hour, one, two, three, four and twenty-four hours. Normally, the clot will remain intact and retain its content of red cells. If fibrinolysin is present the clot will be observed to decrease in size with loss of many of its red cells.

Plasma-saline technic With sterile technic 0.2 cc of citrated plasma is placed in a culture tube with lip (13 by 100 mm), and 5 cc of sterile saline solution added. To this mixture is added 0.2 cc of thromboplastin and 0.2 cc of calcium chloride (0.025-molar) solution, and the contents of the tube are mixed by inversion. Observations are made for lysis of this plasma clot as stated above. This method has advantage over the use of whole blood since the clot can be visualized more easily when the red cells are not present.

Limitations and Interpretations

Fibrinolysin occurs in severe burns and is possibly due to the presence of shock.⁷⁸ It has also been observed after surgical procedures as well as before them.⁸⁴ This observation led to the hypothesis that possibly the release of epinephrine during anxiety states operated as a mechanism for activation of pro-fibrinolysin (plasminogen) normally found in plasma.⁸⁴ This hypothesis has since been tested, and it is possible to develop fibrinolytic activity in circulating blood upon the administration of epinephrine⁸⁵, however, such activity does not develop upon the addition of epinephrine to whole blood in the test tube. Epinephrine release may be the mode of activation of the proteolytic enzyme that is frequently encountered in shock of all types. Since fibrinolysin digests fibrinogen, prothrombin, fibrin and possibly "prothrombin accelerators," there can be maintained, in shock, a vicious circle whereby fibrinolysin causes prolonged hemorrhage with further maintenance of shock and continued production of fibrinolytic activity. In any condition in which hemorrhage is unexplained the stability of the clot should be observed for the presence of fibrinolytic activity.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35451

PRESENTATION OF CASE

A sixteen-year-old schoolboy entered the hospital complaining of constipation.

Three months before entry while at a preparatory school the patient passed half a cupful of red blood one night, soiling his pajamas. A few days later he noted constipation, for which he saw the school nurse, who treated him with mineral oil and an enema. School closed shortly after this, and the patient went home. The constipation continued, and he frequently passed small amounts of semi-solid or liquid feces each day. At times he noted red blood on the toilet tissue and in the bowl. During the summer he worked as a caddie without undue fatigue. He lost 20 pounds, which was ascribed to a more active life and change in diet. For two weeks before entry he had anorexia and nausea in the morning. He also began to have frequent, small bowel movements at night and a dull discomfort in the rectum, which interfered with sleep. He was seen by a physician for a pre-school routine examination. Following this he was sent to the hospital.

The past and family histories were noncontributory.

Physical examination showed a healthy-appearing, well nourished boy. The only positive finding was a hard mass just inside the anus encircling the rectum. No definite ulceration was felt.

The urine was normal. The blood hemoglobin was 15.1 gm, and the white-cell count 10,000. The blood chemical findings were normal.

A barium enema showed partial obstruction in the rectum. Sigmoidoscopy was painful and therefore unsatisfactory, but some hard, red tissue was seen 2.5 cm from the anus, from which a biopsy was taken.

DIFFERENTIAL DIAGNOSIS

DR E PARKER HAYDEN* At first glance this case sounds as if it should be a clear-cut diagnostic problem, and it probably was a clear-cut problem for whoever was in attendance. The story, as far as bleeding is concerned, might suggest almost anything. Bleeding in a sixteen-year-old boy or girl is not common. The usual cause of bleeding in a person that age, in my experience, has been either polyp or fissure. This lad, however, had the symptoms of constipation, and as we read through the history it seems to be a progressive story, with bleeding becoming more frequent. The stools became more fluid, and there was some loss of weight, which I do not believe could be ascribed to the healthy summer occupation of caddying. The average boy would not lose 20 pounds, unless he was very fat, just from caddying in a healthy environment. The onset, two weeks before entry, of anorexia and nausea, together with increasing constipation, suggests a progressive ailment in the rectum. The statement that a definite hard mass was felt low down would suggest that the diagnosis ought not to be difficult, particularly with a biopsy, the result of which we do not have available in this report.

The first thing that one would think of from this description, despite the patient's youth, is a carcinoma of the lower rectum. Carcinoma can occur in a boy of sixteen. I have personally operated upon a boy of seventeen with carcinoma. We know that cancer does occur, usually in association with multiple polyposis, in a fair number of young people. The statement that no ulceration was felt would have to be taken with a grain of salt. One cannot always tell by palpation whether ulceration is present. With frequent movements and bleeding one would expect ulceration, and it probably was present. The normal hemoglobin is a little unusual with a cancer that has been present very long. On the other hand, that is entirely possible. The boy actually did have an annular mass—one that had grown all the way around the bowel wall. It would seem, therefore, that it must have been some sort of infiltrative lesion rather than a benign polyp. In inflammatory stricture there would, of course, be an annular ring, which could be due to tuberculosis or to lymphogranuloma inguinale.

If I were to hazard a guess on this case it would seem to me that carcinoma of the lower rectum was the obvious diagnosis to make on the basis of the résumé, but since it seems so obvious it is very likely something else. It also ran through my mind that he might have had an annular foreign body. A foreign body can produce ulceration, with blood and frequent bowel movements. I think ulcerative colitis can probably be excluded on the basis of the finding of the mass, although the symptoms

*Associate visiting surgeon, Massachusetts General Hospital.

matology of ulcerative colitis and that of cancer are often just about the same, and the latter can occur in the presence of the former

There are other types of tumors that one sees occasionally in the colon, such as lymphosarcoma. If a sarcoma was present it might not be ulcerated, and one would not expect very much bleeding. I think the first diagnosis I would make, however, is carcinoma of the rectum, and if he had a carcinoma of the rectum it would most likely be based on multiple polyposis, although not necessarily so.

Are there any x-ray films available?

DR JOSEPH HANELIN These are films of the barium enema, apparently the only films made. The examiner was loath to put much barium into the bowel because after evacuation there was still a fair amount present, and he was afraid to get too great an accumulation above the lesion. There is clearly demonstrated in these films an annular constrictive lesion involving the rectum, beginning at the anus and going up for 5 or 6 cm. The appearance is quite characteristic of a malignant neoplasm. I would say undoubtedly that it is ulcerated.

DR HAYDEN On the basis of the x-ray report I certainly see no reason to change my first diagnosis. The description of the tissue biopsy would be consistent with carcinoma—a reddened and rather hard bit of tissue. Also the difficulty in proctoscopy is understandable from the degree of narrowing and its proximity to the anal canal, which is sensitive. I do not see how I can make any diagnosis but carcinoma of the rectum, which seems obvious in this case.

A PHYSICIAN Would you consider lymphogranuloma inguinale?

DR HAYDEN That is a lesion in which one does not feel a true mass, although one might get that impression. Lymphogranuloma inguinale is simply an annular inflammatory condition going on long enough to produce scar tissue and gradual narrowing of the rectum. It may take the form of a short diaphragmatic stricture, 10 to 25 cm above the anus, or may produce a tubular stricture.

DR BENJAMIN CASTLEMAN How often does one see rectal stricture in a male patient with lymphogranuloma inguinale?

DR HAYDEN Quite often. Dr Earle Chapman and I gathered together a series of cases of lymphogranuloma inguinale in white people. As I recall it there was a predominance of males, although it has been stated in the literature that females predominate.

DR CASTLEMAN As far as stricture is concerned?

DR HAYDEN I was referring to the incidence of the disease in general.

DR GORDON A DONALDSON Would tuberculosis give this sort of constricting lesion?

DR HAYDEN Tuberculosis of the lower rectum in a hyperplastic form is uncommon. I cannot accurately remember whether I have ever seen one.

The disease usually takes the form of ulceration of the anus, whereas the hyperplastic form is encountered more often in the cecum, though it has been described in the rectum.

DR THOMAS RISLEY I saw this boy first in the office after he was sent in by his doctor. The feeling of the mass was not characteristic of carcinoma. It was extremely rubbery in consistence. It lay just inside the anal ring and on examination was painful. It was not possible to feel an ulceration or a crater. It felt as though the mass were completely covered by mucous membrane, and this was confirmed on introducing the sigmoidoscope. However, some tissue was removed and sent to the laboratory. On the day of operation we had not yet received the report from that tissue and because of the rubbery feeling we biopsied it again in the operating room and waited for a frozen section. On the basis of the frozen section we proceeded with a combined abdominoperineal excision of the rectum. There was a suggestion of lymphoma in the way the tissue felt.

CLINICAL DIAGNOSIS

Carcinoma of rectum

DR HAYDEN'S DIAGNOSIS

Carcinoma of rectum

ANATOMICAL DIAGNOSIS

Colloid carcinoma of rectum, with metastases to regional lymph nodes in a sixteen-year-old boy

PATHOLOGICAL DISCUSSION

DR CASTLEMAN The biopsy showed carcinoma. When we received the entire specimen, there was a large ulcerated tumor that looked like the garden-variety type of adenocarcinoma of the bowel. Microscopically, however, it was not the type of adenocarcinoma that we see ordinarily with well formed glands but a signet-ring-cell type of colloid carcinoma, a type that is more often seen in the stomach. The cytoplasm of each cell was replaced by mucoid material pushing the nucleus to one side to form what is known as a signet-ring cell. This type of tumor is usually a very malignant one. In this particular case the tumor had extended anteriorly to involve the serosa. Sixteen out of seventeen lymph nodes examined were involved.

We had some years ago, I believe, a carcinoma of the bowel, also colloid in type, in a child of seven or eight years. That child came in to the hospital because of a mass in the groin, and on biopsy it proved to be a metastatic lymph node full of colloid carcinoma. The primary site was found in the rectum.

DR HANELIN Was any calcification found?

DR CASTLEMAN I do not believe so.

DR HANELIN The reason I ask this question is that I am thinking of a similar case in which extensive calcification was demonstrated in the x-ray films

CASE 35452

PRESENTATION OF CASE

A seventy-three-year-old housewife was admitted to the hospital because of abdominal pain

Approximately two and a half weeks previous to admission the patient had a sudden onset of severe substernal pain radiating through to the back and associated with dyspnea but no sweating or pallor. She was agitated and in acute discomfort for several hours. For two days following this episode of pain she remained in bed, and the only complaint was nausea with several attacks of vomiting. On the third day after this episode an electrocardiogram showed a small Q wave and inverted T wave in Lead I, with changes in one of the chest leads suggestive of "a small posterior infarct." After ten days of bed rest she became active again and seemed well. Twenty-four hours before admission, following her lunch, she felt somewhat nauseated. An hour or so later she had a sudden onset of persistent vomiting and retching, followed in a short time by urgent watery diarrhea. She gradually developed severe abdominal pain. This was not relieved by morphine administered by a physician, but the nausea and diarrhea subsided somewhat. Several hours before admission the temperature was 102°F. Examination by a physician disclosed a blood pressure of 140 systolic, (?) diastolic, rales at both bases and a diffusely tender abdomen. She was sent to the hospital. During this time she developed a feeling in the left leg as though "her leg had gone to sleep."

Five years before admission the patient had an attack of substernal pressure, pain in both upper arms and dyspnea. She had been seen by a physician, who diagnosed the condition as myocardial infarct. After several weeks of bed rest she resumed activity and was asymptomatic until the present episode.

Physical examination revealed a dehydrated, febrile, seriously ill woman. The thyroid gland was bean-sized and hard. The heart was enlarged 12 cm to the left in the fifth intercostal space. The sounds were of poor quality. There were fine sticky rales throughout the entire right chest up to the midscapula anteriorly and posteriorly on the left, with diminished breath sounds at both bases. The left leg was cool from the hip to the knee and cold from the knee down, it was mottled with bluish discoloration. The left femoral pulse was not palpable. There was some pallor and a greenish tint to the toes. There was moderate abdominal spasm throughout. Peristalsis was diminished and somewhat high-pitched.

The temperature was 102°F, the pulse 110, and the respirations 18. The blood pressure was 90 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 14 gm and a white-cell count of 18,500. The urine had a specific gravity of 1.020 and gave a ++ test for albumin. The sediment contained frequent granular casts, rare red cells and 10 white cells per high-power field. An electrocardiogram was interpreted as showing slight tachycardia and abnormal T and S waves that could be due to coronary disease or to the combined effects of coronary disease and high blood pressure or aortic-valve disease. The T waves were unusually wide, and the QT interval was long. An electrolyte imbalance was suggested.

The patient was given digitalis, and fluid was administered by clysis. Attempts at deflation with a Miller-Abbott tube were unsuccessful. On the third hospital day the blood chloride was 90 milliequiv per liter, the nonprotein nitrogen 64 mg, and the total protein 5.8 gm per 100 cc. The temperature showed a definite upward trend. On the fourth hospital day it was noted that the right femoral artery also was not palpable. The abdomen was distended and had a doughy feel, but peristalsis was audible.

The patient gradually became comatose and died on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR JOHN T. QUINBY* This clinical history is that of a seventy-three-year-old woman with a fatal illness of two and a half weeks' duration. It seems to me that most of the features of this case may be accounted for by a dissecting aneurysm of the aorta, with a number of sequelae that follow very logically from this not too uncommon lesion.

To recapitulate briefly, this woman had, five years before admission, an episode of substernal pressure and dyspnea considered by a physician to have represented a myocardial infarct. I see no reason to doubt that diagnosis. One notes that there was associated pain in both upper arms. Her terminal illness began with severe substernal pain, sudden in onset, with radiation through to the back and dyspnea. This time pain was not experienced in the arms. About two weeks later, she experienced, with fairly sudden onset, an acute and severe abdominal disorder. It was characterized by persistent vomiting and retching followed by urgent watery diarrhea and severe abdominal pain, and a day later a maximum temperature of 102°F. The abdomen showed "moderate spasm throughout", peristalsis was diminished and somewhat high-pitched. Rather rapid pulse and falling blood pressure, to near-shock levels, were noted, though it does not seem from the history that frank clinical shock — that is, peripheral vascular collapse — ex-

*Assistant in medicine, Massachusetts General Hospital.

matology of ulcerative colitis and that of cancer are often just about the same, and the latter can occur in the presence of the former

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that occurs between the end vessels of the systemic arteries and the inferior mesenteric branches

The basal rales extending on the left half way up the chest, in addition to the suggestion of bilateral pleural fluid and the finding of definite cardiac enlargement point to congestive failure. This, I think, can be explained without postulating a further coronary occlusion in the present illness. I think the patient must have had hypertension. In the reported cases of dissecting aneurysm of the aorta this has been an invariable finding. We also are assuming that five years before this episode she suffered a myocardial infarction. The fact that no blood-pressure reading over 140 systolic is recorded during her hospital stay almost certainly is a reflection of the profound prostration going with intestinal infarction and obstruction. Thus I think heart damage by coronary-artery disease and by hypertension manifested itself before the present illness. If tachycardia, fever and azotemia possibly with increased serum potassium level are added to this, cardiac decompensation is understandable. If further coronary occlusion did occur, the most likely mechanism would be a progression of the dissecting aneurysm in a retrograde fashion, as mentioned earlier.

The urinary findings are a good specific gravity of 1.020, a ++ test for albuminuria and frequent granular casts, rare red cells and 10 white cells per high-power field in the sediment. The serum nonprotein nitrogen was 64 mg per 100 cc. Except for the 10 white cells per high-power field in the sediment, there is nothing not entirely compatible with congestive failure and dehydration. Vascular nephritis of more than minimal degree I should doubt to have been present, with a good concentrating power. The moderate azotemia should be classed as pre-renal, I think, and the pyuria—if the leukocytes came from the bladder—could reflect the low-grade cystitis that is almost the rule in elderly women.

The fact that renal function was fairly well preserved does not throw out the diagnosis of dissecting aneurysm of the aorta. Frequently, the renal arteries are not involved though the dissection extends distal to them and in other cases when they are involved renal function has not appeared greatly impaired. The exact anatomical explanation for this is beyond my knowledge to discuss.

The description of the thyroid gland as bean-sized and hard is difficult to interpret. I cannot

see that the clinical history points to thyroid disease of any type. It would seem that the gland was perhaps smaller than normal and harder than normal. An adenoma may have been present, or perhaps this was an involuted gland in an elderly person.

The low serum protein of 5.8 gm per 100 cc is consistent with the patient's nutritional defect combined with her age. The blood chloride value of 90 milliequiv per liter is somewhat below the normal range of 98 to 103 milliequiv and is consistent with the loss of chloride through vomiting and diarrhea. The white-cell count of 18,500 is characteristic of mesenteric thrombosis and bowel infarction.

Electrocardiographic studies in this patient are certainly consistent with the diagnosis of dissecting aneurysm. In this condition the reported findings have been left-axis deviation usually, and a definite pattern of left ventricular strain in a majority of cases. A few cases have shown additional changes suggesting the presence of coronary-artery disease. None of the reported tracings could be considered entirely normal, and yet changes definitely suggestive of an acute myocardial infarct have not been seen, even in cases in which the coronary arteries themselves were involved in the dissection.

The findings in our patient appear to fit well with this experience. The changes in the T waves in Lead 1 and 2 noted on the third day of illness are consistent. Later the tracing showed, besides some tachycardia, abnormal T and S waves, with widening of the T waves and prolongation of the QT interval. An electrolyte imbalance was suggested, as well as an interpretation to the effect that the pattern suggested coronary-artery disease with left ventricular strain. Certainly, some electrolyte disturbance existed, and if with the patient's azotemia there was associated a significant elevation of serum potassium, the widened T waves and increased QT interval may have been due to that. Also, I believe, some coronary-artery disease was present before the onset of the last illness.

CLINICAL DIAGNOSES

- Acute myocardial infarction
- Embolism to mesenteric artery
- Embolism to femoral artery, bilateral
- Acute pulmonary edema
- Congestive failure

isted Three days later the abdomen is described as distended and as having a doughy feel with peristalsis still audible. A guaiac test on the material passed by rectum is not mentioned. A positive guaiac test here would be of interest, and would tend to confirm the impression I get of this acute and progressive abdominal accident — namely that it represented mesenteric-vessel thrombosis with infarction probably extensive, of the bowel. Coming right on the heels of this process occurred another (an arterial) occlusion first in the left leg going on to gangrene and later in the right, without the development of gangrene.

This sequence of events could be well accounted for by a dissecting aneurysm of the aorta beginning either in the ascending or the thoracic portion and extending farther and farther down to include eventually both common iliac arteries in the same morbid process — namely, the creation of an artificial cleavage plane in the media, first of the aorta then of any of its branches to which the dissection extends with resulting marked narrowing of the true lumen and diminution or complete cutting off of the blood flow in the involved vessels. Such a process could also account for occlusion of one or both mesenteric arteries.

The diagnostic problem in cases of this sort is to differentiate dissecting aneurysm of the aorta and coronary thrombosis with myocardial infarction. In my opinion the first is the better diagnosis. I think so for several reasons: first, because almost every fact in the clinical history is consistent with such a diagnosis, and secondly because the sequence of arterial occlusions seems better explained this way. As far as my knowledge goes, the successive occlusion of two major aortic branches (three counting both iliacs) is a very rare event as a sequel to thrombosis on the endocardium, whereas it is very common with dissecting aneurysm. I think that if a very large myocardial infarct were the source of emboli from the heart, the probability of two successive arterial embolizations, both at their origins from the aorta, would be very small. Furthermore, one would have to postulate extensive myocardial damage, I think (in the absence of auricular fibrillation), and here the chances would be that endocardial thrombi would not be limited to the left side of the heart, we have no data on which to base a diagnosis of pulmonary embolism, it seems to me. Finally, I think that the location

of the patient's pain is more characteristic of dissecting aneurysm than of coronary thrombosis. Also with a myocardial infarction severe enough to cause this whole picture the characteristic electrocardiographic pattern should be seen, and it was not present here. For these reasons, I prefer the first diagnosis. The strongest objection to it is the apparent presence of congestive failure. We are led to think of a recent, severe myocardial accident to help explain it, since there is no evidence that failure existed prior to the present illness. As I shall indicate later however, I think it can be accounted for without this supposition. A third possibility is that the aortic dissection proceeded also in a retrograde direction to involve the mouth of at least one coronary artery. This not uncommon sequel may have been present here. I see no way of knowing but I doubt a large, recent myocardial infarction and I think that in any case the occlusive sequelae were in all probability due to dissecting aneurysm of the aorta.

To discuss certain details of the history in the light of a diagnosis of dissecting aneurysm of the aorta, let us consider first the question of the immediate cause of death. With this aortic lesion the terminal event is usually rupture of the aneurysm. This is found to occur into the pericardial sac, with cardiac tamponade into the mediastinum, frequently with hoarseness into one or both pleural cavities, and into the peritoneal cavity, in about that order of frequency. In this case, however, there is little in the clinical history to indicate such an event. Death, I believe, was due to bowel infarction with obstruction, distention, dehydration, azotemia and the presence of congestive failure. Very likely, some peritonitis was present.

Of course an acute abdominal episode of this type with bowel infarction is often precipitated by strangulation of the bowel, as in hernia or volvulus, or by infection in an abdominal organ tributary to the portal vein, as in appendicitis or pelvic infection. In such cases thrombosis usually involves the mesenteric veins. In this patient I believe mesenteric arterial occlusion, probably with thrombosis, is more likely, fitting in with the initial aortic lesion that I have postulated. One or both mesenteric arteries may be involved, if one alone, the superior mesenteric is the more apt to lead to infarction, because of the freer anastomosis

that occurs between the end vessels of the systemic arteries and the inferior mesenteric branches

The basal rales, extending on the left half way up the chest, in addition to the suggestion of bilateral pleural fluid and the finding of definite cardiac enlargement, point to congestive failure. This, I think, can be explained without postulating a further coronary occlusion in the present illness. I think the patient must have had hypertension. In the reported cases of dissecting aneurysm of the aorta this has been an invariable finding. We also are assuming that five years before this episode she suffered a myocardial infarction. The fact that no blood-pressure reading over 140 systolic is recorded during her hospital stay almost certainly is a reflection of the profound prostration going with intestinal infarction and obstruction. Thus, I think heart damage by coronary-artery disease and by hypertension manifested itself before the present illness. If tachycardia, fever and azotemia, possibly with increased serum potassium level, are added to this, cardiac decompensation is understandable. If further coronary occlusion did occur, the most likely mechanism would be a progression of the dissecting aneurysm in a retrograde fashion, as mentioned earlier.

The urinary findings are a good specific gravity of 1.020, a ++ test for albuminuria and frequent granular casts, rare red cells and 10 white cells per high-power field in the sediment. The serum nonprotein nitrogen was 64 mg per 100 cc. Except for the 10 white cells per high-power field in the sediment, there is nothing not entirely compatible with congestive failure and dehydration. Vascular nephritis of more than minimal degree I should doubt to have been present, with a good concentrating power. The moderate azotemia should be classed as pre-renal, I think, and the pyuria — if the leukocytes came from the bladder — could reflect the low-grade cystitis that is almost the rule in elderly women.

The fact that renal function was fairly well preserved does not throw out the diagnosis of dissecting aneurysm of the aorta. Frequently, the renal arteries are not involved, though the dissection extends distal to them, and in other cases when they are involved renal function has not appeared greatly impaired. The exact anatomical explanation for this is beyond my knowledge to discuss.

The description of the thyroid gland as bean-sized and hard is difficult to interpret. I cannot

see that the clinical history points to thyroid disease of any type. It would seem that the gland was perhaps smaller than normal and harder than normal. An adenoma may have been present, or perhaps this was an involuted gland in an elderly person.

The low serum protein of 5.8 gm per 100 cc is consistent with the patient's nutritional defect, combined with her age. The blood chloride value of 90 milliequiv per liter is somewhat below the normal range of 98 to 103 milliequiv and is consistent with the loss of chloride through vomiting and diarrhea. The white-cell count of 18,500 is characteristic of mesenteric thrombosis and bowel infarction.

Electrocardiographic studies in this patient are certainly consistent with the diagnosis of dissecting aneurysm. In this condition the reported findings have been left-axis deviation usually, and a definite pattern of left ventricular strain in a majority of cases. A few cases have shown additional changes suggesting the presence of coronary-artery disease. None of the reported tracings could be considered entirely normal, and yet changes definitely suggestive of an acute myocardial infarct have not been seen, even in cases in which the coronary arteries themselves were involved in the dissection.

The findings in our patient appear to fit well with this experience. The changes in the T waves in Lead 1 and 2 noted on the third day of illness are consistent. Later the tracing showed, besides some tachycardia, abnormal T and S waves, with widening of the T waves and prolongation of the QT interval. An electrolyte imbalance was suggested, as well as an interpretation to the effect that the pattern suggested coronary-artery disease with left ventricular strain. Certainly, some electrolyte disturbance existed, and if with the patient's azotemia there was associated a significant elevation of serum potassium, the widened T waves and increased QT interval may have been due to that. Also, I believe, some coronary-artery disease was present before the onset of the last illness.

CLINICAL DIAGNOSES

- Acute myocardial infarction
- Embolism to mesenteric artery
- Embolism to femoral artery, bilateral
- Acute pulmonary edema
- Congestive failure

DR QUINBY'S DIAGNOSES

Dissecting aneurysm of aorta
 Occlusion and thrombosis of mesenteric arteries,
 one or both
 Infarction and gangrene of bowel, probably both
 small and large intestine
 Peritonitis?
 Occlusion of left common iliac artery, total
 Occlusion of right common iliac artery, incom-
 plete
 Gangrene of left leg and foot
 Generalized arteriosclerosis
 Arteriosclerotic and hypertensive heart disease,
 with old coronary thrombosis and myocardial
 infarction, and ? recent coronary occlusion
 Adenoma of thyroid gland?
 Pulmonary edema
 Hydrothorax, bilateral

ANATOMICAL DIAGNOSES

*Coronary thrombosis, recent, left anterior descending
 branch*
*Myocardial infarction, left ventricle, recent, with
 mural thrombus*
*Embolization, multiple, of superior mesenteric and
 femoral arteries*
Gangrene of ileum
 Peritonitis, purulent, generalized
 Bronchopneumonia, lower lobes of lung
 Arteriosclerosis, generalized
 Nontoxic nodular goiter

PATHOLOGICAL DISCUSSION

DR DAVID G FREIMAN Upon opening the abdomen we noted that the omentum, loops of small bowel and portions of the large bowel were matted together by a thick yellow exudate, and a small amount of gray, murky fluid lay free in the pelvis. The jejunum and proximal third of the ileum were moderately dilated and congested. Beyond this

point the ileum became gradually less distended, pale and friable, and a few scattered patches appeared dark and necrotic. The lowermost portion of the ileum and the large bowel, though flabby, showed no obvious gangrene. The cause of the gangrene in the small bowel was a reddish-gray, adherent embolus in the superior mesenteric artery, which extended from the point of origin of the ileocolic artery distally for a distance of about 2 cm. Both inferior and superior mesenteric veins contained adherent laminated thrombi extending distally into the smaller tributaries. These were undoubtedly secondary to the intestinal necrosis. Emboli were also present in both femoral arteries extending distally from the level of the inguinal ligaments. That on the right was slightly adherent and encroached upon the profunda branch. Both arteries below the points of occlusion showed severe sclerosis to the point of marked narrowing, but the lumens were patent. Thus, practically all Dr Quinby's diagnoses relating to the abdomen were confirmed. The arterial occlusions were due, however, not to an aortic dissection but to an unusual multiple embolization, a source for which was found in the heart. A recent myocardial infarction involved the anterior apical and part of the adjacent lateral walls of the left ventricle, and a mural thrombus about 3.5 cm in diameter was adherent to the endocardium in the region of the apex. About 1.5 cm below the point of origin of the descending branch of the left coronary artery, a recent occlusion was present. The left circumflex and right coronary arteries were sclerotic to the point of marked narrowing in several areas, but were not occluded. The lungs showed marked congestion in the posterior and inferior portions of the lower lobes, and microscopical examination revealed bronchopneumonia in these areas. There was no pleural fluid. The thyroid gland contained several small cystic nodules.

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MEDICAL EDUCATION AT MESA VERDE

ONE of the pictorial magazines recently presented a photograph of the governors of Utah, Colorado, Arizona and New Mexico, seated at a table placed over the exact spot where the boundaries of these four states meet. It would be of interest to know what they had to say to each other if anything, about medical education.

The ratios of the 1949 freshman medical students to the populations for these four states swing from the very highest to the very lowest in the United States. The ratios for all the states are shown in the September 3 issue of the *Journal of the American Medical Association*. Utah is the highest, with 10.5, New Mexico is the lowest, with 1.5, Colorado and Arizona are 7.6 and 3.1 respectively. Or one might similarly arrange a luncheon table at the point where the boundaries of Wyoming, South Dakota and Nebraska converge, the ratios for these three states being 2.6, 6.6 and 8.9.

In the same number of the *Journal* it was editorially suggested that these discrepancies had been noted in Washington, and it was pointed out that the bill for federal aid to medical schools now pending before the Senate provides, "No payments may be made to any school unless such school has filed an application therefor which contains adequate assurance, as determined by the Surgeon General that such school provides and will provide reasonable opportunity for the admission of out-of-state students." Under date of September 2 the American Medical Association also released a statement to the press under the caption "Residency Limitations by Medical Schools Held to be Disservice." In this statement it is pointed out that although tax-supported institutions might be expected to render their major services to the community that supports them, the exclusion of all nonresident students may not prove to be in the best interest of the community or the region of which the community is a part.

When the ratios quoted above are plotted geographically, it is plain that it is a regional problem, and could be more satisfactorily met by regional arrangements than if every medical school were prevailed upon to open wide its doors to all comers. At least it seems appropriate for a substantial majority of the medical students in the United States to be able to receive their professional training within a reasonable distance of their places of residence. There may be good reasons why certain persons want to cross the continent for purposes of study, and there may be good reasons for certain schools to want their students to be gathered from widely dispersed areas, but it is hard to believe that any state has five times as many qualified candidates as its next door neighbor. It is probable that the admission authorities of the medical schools are sensitive to and sympathetic with their regional needs, but the ultimate authority of tax-supported institutions may rest in governmental bodies. Regional consciousness is a difficult thing for politicians to acquire, particularly at what is known as the "state level." More dinners, or card games, or whatever it is that governors do when they meet at Mesa Verde might prepare them to carry back to their legislatures a far-sighted

point of view toward their whole region as well as their individual states. This kind of leadership would help.

In the meantime probably every medical school in the country would be doing itself a good turn if it were to encourage application from residents of the states with the lowest ratios of medical students to populations.

PEACETIME USO

MR. KARL K. VAN METER, executive vice-president of the United Service Organizations, consisting the YMCA, National Jewish Welfare Board, Salvation Army, National Catholic Community Service, YWCA and National Travelers Aid Association, points out the need for reactivating the USO now, in peacetime, and urges that funds be raised privately or through the agency of local community chests for this purpose.

With the present armed forces numbering over one and one-half millions, 70 per cent or more below the age of twenty-one, the desirability of some sort of benevolent civilian influence is evident, perhaps to an even greater extent than in wartime. Then the nearness of actual danger furnished incentive enough to serve. Military service in time of peace, however, directed as it is to warding off a more distant danger, leaves the individual service-man's incentive to be largely derived from the appreciative attitude of the public with whom he comes in contact. The responsibility of strengthening the armed forces has been rightly accepted, and with it goes the responsibility for their spiritual and social welfare.

It may be asked why this job should be done by volunteer workers on privately raised funds (the goal is twelve million dollars) rather than being included in the military budget, of which it would be an infinitesimal fraction, and it will come as a surprise to those who associate President Truman's name with the "Welfare State" to learn that a letter urging the former method appears in Mr. Van Meter's brochure over the signature of Harry Truman himself. Regardless of how efficient the military establishment has been, is now or may become, experience and common sense show that the

part of a soldier's morale that depends on his contact with his civilian background and surroundings cannot be supplied by military officialdom. The nation wants its sons efficiently trained and disciplined for national defense, but during their training at home or abroad it wants them "in contact with the normal and wholesome activities of civilian life" so they will not return "bitter and disillusioned, resentful of the treatment they have received from civilians." Furthermore "much of USO activity is of a religious and spiritual nature which no governmental auspices could appropriately provide."

Mr. Van Meter makes out so unanswerable a case for reactivating the USO now, four years after the ending of the war, that one cannot help wondering why so little has been done about it before.

POLIOMYELITIS GOES UNDERGROUND?

THE virus of poliomyelitis, according to a hypothesis recently advanced by L. E. Rector,* of St. Louis, may quite literally go underground. This hypothesis is based on the assumption that any single host or vector of poliomyelitis must fulfill certain criteria. It must be found throughout both the temperate and tropical zones, it must account for the frequently observed tendency of the disease to begin and to have a higher incidence in rural than in urban communities, it must account for the seasonal tendency of the disease in man, and it must be so inconspicuous as to have escaped consideration to date.

The ground mole, happy hero of all the creatures that people the damp and sunless habitations found in Kenneth Grahame's *The Wind in the Willows*, fulfills these requirements. Voracious, ever on the forage, the mole adapts the level of his burrowing to that of his natural quarry, the earthworm. In the winter his runs are deep in the earth, in the summer so shallow as barely to be covered by the roots of the overlying vegetation. If a true representative of the grass roots is wanted, it will be the mole. Persons lying on the ground in the summer, whether in park or pasture, may be cultivating the acquaintance of the mole to a degree that invites even the transfer of a virus.

*Rector, L. E. Mole as possible reservoir of poliomyelitis. *Arch. Path.* 47:366-377, 1949.

Because of the hypothetical possibility that the mole might be the host of poliomyelitis, moles from Forest Park, St. Louis, were made the subjects of an investigation into their susceptibility to the virus. A number having been injected intracerebrally with filtrates of infected mouse brains or with stool filtrates from child victims of the disease were kept under observation.

Various clinical signs were recorded, including anorexia, cardiac arrhythmias consisting of dropped beats and extrasystoles, and coming to the surface to die—an unnatural procedure for moles. At autopsy no lesions typical of poliomyelitis were found, but this lack of pathology is found also in rabbits subjected to inoculation with the virus.

In the unremitting search for the method of spread of infantile paralysis, each possibility must be explored. There is as yet no proof that the mole carries the virus of the disease, but there is also no proof that it does not.

RETIREMENT OF DR. FAXON

THE Massachusetts General Hospital's traditional "Ether Day" celebration was made this year the occasion for an inspired farewell party to the retiring director, Dr. Nathaniel Wales Faxon. Dr. Faxon's eminence as one of the country's leading hospital directors was emphasized by various speakers, and the fact was not lost sight of that he had begun his career as a country doctor in Stoughton, Massachusetts.

This breadth of experience is enough in itself to make the *Journal*, in wishing him a happy "retirement," hope that it will not be too retired. His services to the community as an elder statesman will be so valuable that he will, no doubt, not be permitted to become bored with idleness between his fishing trips.

Important advances are daily made in the dental art. Colleges, based upon the best and most thorough principles, are springing up in various sections of the States. Indeed, the progress of this science here is attracting much attention in England and on the Continent of Europe, and amongst those things in which we can boast a pre-eminence over the old world, may be safely enumerated dental surgeons.

Boston M. & S. J., November 7, 1849

NOTES FROM THE MEDICAL EXAMINER

USE OF BLOOD GROUPS IN CASES OF DISPUTED PATERNITY

The application of blood groups in cases of disputed paternity depends upon the fact that the laws of their inheritance are accurately known. Thus, neither antigen A nor antigen B will appear in the blood of a child unless it was present in the blood of at least one of the child's parents. In addition, 2 persons of Group O will never produce a child of Group AB. Conversely, 2 persons of Group AB will never produce a child of Group O. Table 1

TABLE 1 *Combinations Allowing an Alleged Father to Establish Nonpaternity**

PUTATIVE FATHER BLOOD GROUP	KNOWN MOTHER BLOOD GROUP	KNOWN CHILD BLOOD GROUP
O	O	A B
O	A	B AB
O	B	A AB
O	AB	AB
A	O	B
A	A	B AB
B	O	A
B	B	A AB
AB	O	O
AB	A	O
AB	B	O

*Impossible mother-child combinations are not included

shows the possible outcome of the various types of mating.

The application of these laws in forensic medicine is extremely simple. If a man is alleged to be the father of an illegitimate child, it is only necessary to test his blood, the blood of the child and the blood of the mother. If the mother is Group O, the alleged father Group O, and the child Group A and Group A antigen is not present in the blood of the alleged father or of the mother, it could not have come from the mother, it must have come from the real father of the child. Therefore, it may be concluded that the alleged father is not the natural father.

On the other hand, if the mother and the alleged father are Group A and the child is Group O, this does not prove that the alleged father is not the real father of the child, because persons of Group A sometimes produce children of Group O (Table 1). The O factor seems to act as a recessive in the presence of A or B. If these simple rules are kept in mind, little difficulty will be encountered in interpreting the results.

In performance of the tests it is naturally very important that the blood be correctly identified at the time it is taken. Sufficient blood may be taken by puncture of the finger or earlobe of the man and woman and put into physiologic saline solution. With very young children puncture of the great toe seems preferable.

The A and B antigens are not the only ones that may be applied to the investigation of paternity.

point of view toward their whole region as well as their individual states. This kind of leadership would help.

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Holbrook, 1, Holden, 3, Holyoke, 3, Hudson, 1, Ipswich, 2, Kingston, 1, Lancaster, 4, Lawrence, 2, Lee, 2, Lenox, 1, Leominster, 5, Lexington, 4, Longmeadow, 2, Lowell, 1, Ludlow, 1, Lynn, 24, Malden, 7, Manchester, 2, Mansfield, 6, Marhlehead 3, Marion, 2, Marlboro, 1, Marshfield, 1, Medford, 15, Melrose, 17, Mendon, 2, Methuen, 1, Middleboro, 1, Milford 1, Mills, 1, Milton, 3, Montague, 1, Nahant, 1, Natick, 4, Needham, 3, New Bedford, 6, Newburyport, 3, Newton, 11, North Attleboro, 2, North Brookfield, 2, North Reading, 3, Northampton, 2, Norton, 2, Norwell, 2, Norwood, 4, Palmer, 3, Peabody, 3, Pembroke, 2, Pittsfield, 10, Plymouth, 3, Quincy, 19, Randolph, 4, Reading, 4, Revere, 5, Rochester, 1, Rockland, 4, Salem, 7, Sayov, 1, Scituate, 1, Sharon, 5, Shirley, 3, Shrewsbury, 1, Somerville, 9, South Hadley, 1, Southboro, 2, Spencer, 1, Springfield, 4, Stockbridge, 1, Stoughton, 2, Stow 1, Swampscott 2, Swansea, 1, Taunton, 2, Tewksbury, 1, Townsend, 1, Truro, 1, Wakefield, 5, Walpole, 1, Waltham, 13, Watertown, 5, Wellesley, 3, West Boylston, 1, West Springfield, 1, Westfield, 3, Westford, 2, Westminster, 4, Weston, 1, Westport, 3, Westwood, 1, Weymouth, 6, Winchendon, 2, Winchester, 4, Winthrop, 6, Woburn, 4, Worcester, 30, Wrentham, 1, total, 608

Salmonellosis was reported from Boston, 3, Lexington, 2, Lowell, 1, Marhlehead, 1, total, 7

Septic sore throat was reported from Boston, 3, Westford, 1, Worcester, 1, total, 5

Trichinosis was reported from Boston, 2, Brockton, 1, Malden, 2, Plymouth, 1, Worcester, 3, total, 9

Undulant fever was reported from Great Barrington, 1, Holden, 1, total, 2

MISCELLANY

AN APPEAL TO WHO

The editors of *Ärztliche Praxis*, a German weekly medical journal devoted to the interests of the general practitioner, have directed an open letter for help to Dr Brock Chisholm, director general of the World Health Organization

The appeal is based on the surplus of skilled physicians in the three western zones of Germany and their lack in many other parts of the world and the desire that the World Health Organization may facilitate the emigration of these trained physicians into less favored areas

CORRESPONDENCE

LAST REBUTTAL

To the Editor: Dr Allan M. Butler's letter in the October 13 issue of the *Journal* hints that Dr McManamy's aversion to "therapeutic" abortion, euthanasia and so forth is used as an "out" in avoiding difficult problems. It seems to me that euthanasia and "therapeutic" abortions are definite acts performed expressly to avoid difficult problems.

I suggest that Dr Butler should find out what "good Catholicism" means before he uses the term.

Unlike many things, the Fifth Commandment has no exceptions.

FRANCIS D. MCCARTHY, M.D.

Melrose, Massachusetts

BOOK REVIEWS

A Treatise on Obstetric Labor. By Richard Torpin, M.D. With a chapter on erythroblastosis fetalis and the Rh factor, by Edith L. Potter, M.D., and Philip Levine, M.D. 8°, cloth, 590 pp., with 187 illustrations. Augusta, Georgia: Augusta Obstetric and Gynecologic Book Company, 1949. \$7.00.

This treatise on obstetric labor is dedicated to the praiseworthy proposition that there are far too many operative deliveries and that a much larger percentage of labor should be normal. This, the author believes, can be accomplished by a judicious use of fluids, dextrose, transfusions, oxygen, sedation and rest, and in thousands of cases he has found these measures "far more profitable in saving life and preventing

disability of mother and fetus than surgical treatment immediately and ever so skilfully done."

In a series of 41 chapters and 73 selected illustrative case reports he undertakes to demonstrate this proposition. As a result of his experience, he has almost entirely eliminated from his practice haggling, extraction and version, though rather surprisingly he performs episiotomy in almost every case, including normal deliveries. This conservative attitude which he attributes to his early training by Culbertson and Heaney at Rush Medical College, is at least a refreshing contrast to much modern radical surgical obstetric teaching.

There is an authoritative chapter on erythroblastosis fetalis and the Rh factor by Dr Edith L. Potter and Dr Philip Levine. The work is illustrated with 187 admirable figures. Twelve hundred references to the literature are distributed in appropriate bibliographic groups at the close of the chapters.

Gynecologic Diagnosis. By Robert Tauher, M.D. 8° cloth, 275 pp., with 80 illustrations. New York: Thomas Nelson and Sons, 1949. \$5.00.

This monograph is intended to teach students correct methods of gynecologic diagnosis. The author first discusses history taking and interpretation, the various techniques of physical examination, the essential laboratory tests and the common diagnostic surgical procedures. He then presents what he terms a diagnostic clinic, a series of 33 cases in six groups, illustrating a number of frequent and a few rare pathologic conditions. At no time is the diagnosis stated, but the reader is supposed to make his own and then to refer to a list at the end of the book. There is an excellent final chapter on errors in diagnosis, and their avoidance. The work is admirably illustrated with eighty full-page figures by C. W. Brill, and has a brief bibliography of seventeen appropriate special references.

Die Kreuzschmerzen der Frau ihre Deutung und Behandlung. *Gynäkologische Orthopädie*. By Professor Dr Heinrich Martius, director of the University Women's Clinic, Göttingen. Third edition. 8°, paper, 136 pp., with 64 illustrations by Käthe Drosen. Stuttgart: Georg Thieme, 1947. Imported by Grune and Stratton, Incorporated, New York. \$2.75.

This third edition of a well known work, first published a decade ago, by the director of the Women's Clinic at Göttingen, presents an exhaustive survey of all the gynecologic conditions to which sacral pain in women is commonly attributed. Without denying the importance of these and of their appropriate treatment, the author believes that in all cases there is also an intrinsic postural element—that sacral, lumbosacral and sacroiliac pain in women is fundamentally an orthostatic symptom whose concurrent orthopedic treatment with a properly designed and adjusted girdle is essential, if satisfactory and total relief is to be obtained.

The book is well illustrated with 64 admirable black-and-white drawings by Käthe Drosen, and has an elaborate and valuable bibliography of 500 well selected references.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Surgery of the Eye. By Meyer Wiener, M.D., honorary consultant, ophthalmology, Bureau of Medicine and Surgery, United States Navy. Second edition. 8°, cloth, 426 pp., with 426 illustrations. New York: Grune and Stratton, 1949. \$12.00.

In this second edition a special illustrated work on surgery of the eye, first published in 1939 and long out of print, has been revised and brought up to date. The new material includes the preparation of sutures preliminary to the incision for cataract, Otto Barkan's improved technic for congenital glaucoma, Burch's method of implantation in exsiccation and Wiener's method of transplantation of the cornea by means of a mechanically obtained leveled edge. The text is not padded with redundant references to the literature. There is a good index. The work is intended to be a handy atlas of operating procedures for the ophthalmologist.

The inheritance of the M and N factors (Table 2), discovered in 1927, is equally well known

The rules of inheritance are somewhat simpler because there is nothing corresponding to Type O—that is, either antigen M or antigen N, or both, is always present in the blood. The interpretation of the test is otherwise exactly the same.

The Rh factors, discovered in 1940, have been investigated sufficiently so that they are being used by some workers in cases of disputed parentage. Eight genes are thought to be involved in the inheritance of the Rh factors, and since the resulting combinations of these genes, 2 at a time, give a pos-

TABLE 2 Exclusion of Paternity on the Basis of Characteristics M and N

CHILD CHARACTERISTIC	MOTHER CHARACTERISTIC	FATHER NOT POSSIBLE CHARACTERISTIC
M	M or MN	N
N	N or MN	M
MN	M	M
MN	N	N

sible 36 genotypes, not all of which can be distinguished by the use of the serums at present available or even by the use of any serums that may eventually be available, it is not so easy to summarize the interpretation of tests for the Rh factors in cases of disputed parentage. Weiner's summary of the situation is as follows:

Factors Rh₀, rh', rh'', hr' and hr'' cannot appear in the blood of a child unless present in the blood of one or both parents.

Parents of types Rh₁Rh₁ and rh'rh' cannot have children of types rh, Rh₀, Rh₂ or rh'', and parents of types rh, Rh₀, Rh₂ and rh'' cannot have children of types Rh₁Rh₁ or rh'rh'. Or, more simply, hr'-negative parents cannot have rh'-negative children, and rh'-negative parents cannot have hr'-negative children.

Parents of types Rh₂Rh₂ and rh''rh'' cannot have children of types rh, Rh₀, Rh₁ and rh', and vice versa. Or, more simply, hr''-negative parents cannot have rh''-negative children, and rh''-negative parents cannot have hr''-negative children.

WILLIAM C. BOYD, M.D.

Professor of Immunochemistry, Boston University School of Medicine

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1949

RÉSUMÉ

DISEASES	SEPTEMBER 1949	SEPTEMBER 1948	SEVEN YEAR MEDIAN
Chancroid	2	2	1*
Chicken pox	85	135	114
Diphtheria	7	27	11
Dog bite	1009	980	924
Dysentery, bacillary	5	9	11
German measles	48	58	56
Gonorrhea	292	303	410
Granuloma inguinale	1	0	0*
Lymphogranuloma venereum	1	1	1*
Malaria	1	1	13
Measles	48	203	150
Meningitis, meningococcal	2	4	6
Meningitis, Pfeiffer bacillus	0	2	1
Meningitis, pneumococcal	0	1	1
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	1	0
Meningitis, undetermined	2	6	4
Mumps	173	351	197
Poliomyelitis	608	55	121
Salmonellosis	7	2	20
Scarlet fever	56	105	190
Syphilis	155	141	352
Tuberculosis, pulmonary	196	200	205
Tuberculosis, other forms	8	14	15
Typhoid fever	0	1	2
Undulant fever	2	4	2
Whooping cough	463	268	520

*Five-year median

COMMENT

Diseases above the seven-year median for September were dog bite and poliomyelitis.

Diseases below the seven-year median were chicken pox, German measles, measles, mumps, salmonellosis, scarlet fever and whooping cough.

Poliomyelitis continued at a high level, exceeding all records for September except 1916. If only paralytic cases were counted, however, the figures this year were far below 1916.

Although chicken pox was unusually prevalent during the first half of this year, it fell to the lowest level for this month since 1939.

Measles also ran unusually high during the early part of this year, but the number of cases fell to the lowest September since 1937.

Scarlet fever, for the past three months, has been at the lowest levels ever recorded.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from New Bedford, 1, total, 1.
Diphtheria was reported from Boston, 1, Chelsea, 1, Foxboro, 1, Lenox, 1, Malden, 1, Rockport, 1, Somerville, 1, total, 7.

Dysentery, amebic, was reported from North Andover, 1, total, 1.

Dysentery, bacillary, was reported from Boston, 4, Brookline, 1, total, 5.

Encephalitis, infectious, was reported from New Bedford, 1, Salisbury, 1, total, 2.

Lymphocytic choriomeningitis was reported from Springfield, 1, total, 1.

Malaria was reported from Medford, 1, total, 1.

Meningitis, meningococcal, was reported from Brockton, 1, Malden, 1, total, 2.

Meningitis, undetermined, was reported from Haverhill, 1, Worcester, 1, total, 2.

Poliomyelitis was reported from Abington, 1, Adams, 1, Amesbury, 2, Amherst, 3, Arlington, 11, Ashby, 3, Ashland, 1, Attleboro, 4, Auburn, 1, Ayer, 1, Barnstable, 2, Bellingham, 1, Belmont, 1, Berlin, 1, Beverly, 8, Billerica, 2, Boston, 87, Braintree, 6, Brewster, 1, Brockton, 5, Brookline, 10, Burlington, 1, Cambridge, 5, Canton, 3, Carver, 1, Charlton, 2, Chelsea, 7, Chicopee, 1, Clinton, 1, Cohasset, 1, Concord, 4, Dalton, 1, Dedham, 4, Dennis, 1, E Bridgewater, 3, Everett, 15, Fairhaven, 1, Fall River, 6, Framingham, 6, Framingham, 3, Franklin, 1, Great Barrington, 1, Groveland, 1, Hampden, 1, Haverhill, 2, Hardwick, 1, Hatfield, 1, Haverhill, 5, Hingham, 4,

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THE GENESIS OF HEART SOUNDS

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CORDOBA, ARGENTINA

IT IS possible that the existence of the heart sounds was known to Hippocrates¹ and even that he made use of his knowledge for diagnostic purposes, but William Harvey² seems to have been the first to make specific reference to them. "With each movement of the heart as a quantity of blood is delivered from the veins to the arteries, a pulse takes place, which may be heard in the chest."

It is rather astonishing that the physicians of that time had thus far paid no attention to the heart sounds, but it is even more astonishing that their existence, when pointed out by Harvey, was soon denied. It was Parisanus³ who said, "Neither we, poor deafts nor any other doctor in Venice can hear them, but happy he is who can hear them in London."

Although Harvey placed beyond doubt the existence of sounds accompanying the heart's activity, Laënnec⁴ nearly two centuries later, gave the first precise description of the character of the sounds in normal and pathologic conditions and founded the art of auscultation.

Once the existence of the heart sounds was established, their cause was sought, and thus began an interminable series of investigations, controversies and theories, which have not ceased even at the present time. Theories on the causes of the heart sounds multiplied at such a rate that in 1881 Sandborg⁵ collected no less than forty, most of which were entirely without clinical or experimental basis and often revealed a complete ignorance of cardiac physiology on the part of their originators.

The first serious attempts to elucidate the exact causes of the heart sounds were made from 1835 on by various committees appointed by the British Association for the Advancement of Science.⁶ The problem was studied experimentally, and many of the findings have since become classic, such as the experiments on the part played by the ventricular muscle in the causation of the first sound. These studies were of the greatest value in that they clarified the whole problem, mainly by demonstrating the absurdities of most of the current theories of the day.

The advent of the graphic methods of recording soon made possible a more precise analysis of the different phases of cardiac activity and afforded a method that allowed one to ascertain the exact moments of production and other peculiarities of the heart sounds.

The time relations between heart sounds and cardiac events was an additional contribution to the elucidation of the causes producing the heart sounds.

It is now certain that at least four sounds may occur, under normal conditions, during the heart cycle. Two of them, the classic first and second sounds, are heard on any living person. A third heart sound may be heard during early diastole in many young persons after the second sound, and the fourth sound, also called auricular, takes place and may often be heard immediately before the first sound during auricular systole.

THE FIRST HEART SOUND

The first heart sound is certainly a complex phenomenon, and although there is no general agreement concerning the conditions that produce it, there is no doubt that they are numerous. In fact such a multiplicity of causes explains most of the discrepancies existing between the findings of different investigators. Each investigator, using some special technic, has taken account only of the factors that his own particular method revealed, and has ignored the existence of all that it was unable to detect. Here, as elsewhere in science, the existence of such discrepancies is a clear demonstration of incomplete knowledge of the subject, and this is due largely to inadequacy of the procedures employed. With improvement in technic a more objective study can be made, discrepancies gradually disappear, and knowledge of the subject becomes solid and well founded.

There is experimental and clinical evidence that the following events produce vibrations contributing to the formation of the first sound: muscular contraction and tension of the ventricular walls at the onset of ventricular systole (muscular factor), closure of the auriculoventricular valves (valvular factor), movements and distention caused by the

*Visiting professor in physiology, Long Island College of Medicine; director, Instituto de Investigacion Medica, Mercedes y Martin Ferreyra.

Critical Studies in Neurology By F M R Walshe, M.D., F.R.S., F.R.C.P., physician to University College Hospital, physician to the National Hospital for Nervous Diseases, Queen Square, and fellow of University College, London 8°, cloth, 256 pp., with 16 illustrations Baltimore Williams and Wilkins Company, 1948 \$4.50

The author has brought together in this small volume six papers originally published in *Brain* during the period 1942 to 1947, to which is added a paper published in the *British Medical Journal* in 1945. The series is preceded by an essay entitled "The Function of Criticism in Medicine." The reprinted papers comprise the anatomy and physiology of cutaneous sensibility, the giant cells of Betz, the motor cortex and the pyramidal tract, the mode of representation of movements in the motor cortex with special reference to "convulsions beginning unilaterally" (Jackson), the notion of the "discrete movement" in willed motion, the role of the pyramidal system in willed movements, and the integration of medicine. The publishing is well done. It is a convenience to have the scattered papers of Dr. Walshe brought together in one volume. It should be in the neurologic sections of medical libraries and available to neurologists.

Diseases of the Fundus Oculi With atlas By Adalbert Fuchs, M.D., co professor of ophthalmology of the University of Vienna. Translated by Erich Pressburger, M.D. Edited by Abraham Schlossman, M.D. First English edition 4°, cloth, 381 pp., with 81 illustrations and 44 tables Philadelphia Blakiston Company, 1949 \$30.00

It is a pleasure to note that this classic treatise of Professor Fuchs has been translated into English. The original German edition appeared in 1943, and in this edition in English the author has added many pictures and much material that had not appeared before either in German or in English, making it practically a new work. There are eighty figures in the text and the appended atlas consists of forty-four plates in color printed from the original plates in Vienna, and imported for inclusion in this volume. The plates are typical of the finest German work. There is a good index, and the type and printing are excellent. Dr. Fuchs is well known for his *Atlas of Histopathology of the Eye*, published in two volumes in 1923 and 1927. The edition is limited to 995 numbered copies. The price is not excessive for this type of book. The atlas should be in all eye collections in medical libraries and likewise available to all ophthalmologists.

NOTICES

COMBINED MEETING OF NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE AND MASSACHUSETTS CHAPTER OF AMERICAN PHYSICAL THERAPY ASSOCIATION

A combined meeting of the New England Society of Physical Medicine and the Massachusetts Chapter of the American Physical Therapy Association will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Wednesday, November 16, at 8 p.m.

Dr. Eugene E. Record will speak on the subject "The Amputee and His Rehabilitation," with lantern slides, motion pictures and case presentations. Dr. Arthur L. Watkins will lead the discussion.

Physicians, physical therapists, occupational therapists and corrective therapists are cordially invited to attend.

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The eighth lecture will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Thursday, November 17, at 8 p.m.

Dr. Elvin Semrad will speak on the subject "Common Pitfalls in Psychotherapy."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will also be shown during this period.

MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

The annual fall meeting of the Massachusetts Public Health Association will be held at Simmons College, 300 Fenway, Boston, on Thursday, November 17. The section meetings, which begin at 4 p.m., will include sessions of the sections of health officers, laboratory, sanitation, maternal and child health and public-health nursing, health education and food and nutrition. The dinner session will be held at 6 p.m. The feature of the general session, beginning at 7 p.m., will be a panel discussion, led by Dr. John F. Conlin, on the subject "How John Q. Boston Was Persuaded To Be X-Rayed," which will emphasize the need of community participation in the attainment of public-health objectives.

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Tuesday, November 22, at 8 p.m. The following medical and surgical program by the Lahey Clinic, with Dr. Frank H. Lahey in charge, will be presented:

The Selection of Patients for Sympathectomy for Hypertension (Including Results after Operation) Dr. James A. Evans

The Management of Ulcerative Colitis Dr. Everett D. Kiefer

Blood Diseases Related to the Spleen, and Indications for Splenectomy Dr. John W. Norcross

Recent Advances in the Management of Thyroid Diseases Dr. Frank H. Lahey

There will be a short business meeting.

Subsequent meetings will be held on Tuesday, January 24, Tuesday, February 28, Tuesday, March 28 and Wednesday, May 3 (annual dinner).

JOINT MEETING OF ALPHA OMEGA ALPHA AND BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A lecture will be given under the joint sponsorship of the Harvard Chapter of Alpha Omega Alpha and the Boston City Hospital House Officers' Association in the auditorium of Building E, Harvard Medical School, on Tuesday, November 22, at 5 p.m.

The lecture will be on "Compound E in Arthritis" and will be delivered by Dr. Philip S. Hench, head of section in Division of Medicine, Mayo Clinic, and associate professor of medicine, The Mayo Foundation.

WORCESTER COUNTY CHAPTER, MASSACHUSETTS HEART ASSOCIATION

A panel discussion sponsored by the Worcester County Chapter of the Massachusetts Heart Association will be held at Dean Hall, Worcester, on Tuesday, November 22 at 8 p.m. The subject will be "The Problem of the Cardiac in Industry."

Howard B. Sprague, M.D., of Boston, president-elect of the American Heart Association, will be chairman of the panel. The panel speakers will include Eugene H. Giroux, chairman of the Massachusetts Industrial Accident Board, Karl Benedict, M.D., industrial physician, Norton Company, Worcester, who will speak on the subject "The Viewpoint of an Industrial Physician," and two members of the Worcester County Bar Association, who will present legal angles.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The eighth annual meeting of the American Academy of Dermatology and Syphilology will be held in Chicago from December 3 through December 8.

The principal sessions will be held at the Palmer House, with special courses in histopathology and mycology scheduled for Saturday and Sunday, December 3 and 4, at the medical schools of the University of Illinois and Northwestern University. Teaching clinics will be held at the University of Illinois College of Medicine in Chicago on the afternoons of December 5, 6 and 7.

(Notices concluded on page xvii)

of the valvular factor for the production of the heart sounds

No matter how obvious it seems to consider the vibrations of the valves as a main cause of the heart sounds, dissident views have also appeared. Just as an example of how positive a man can be in affirming or denying the role of the heart valves in the production of the heart sounds Kassatkine,²¹ a Russian investigator considered himself justified in concluding that "the tendency to consider the heart sounds as a valvular sound is a mistake." He believes that the view of those who attribute the origin of the sounds to the vibrations of the heart walls and of the walls of the aorta and pulmonary arteries adjacent to the valvular orifices is more convincing.

Vascular Component

Even in the earliest writings on the subject, the idea was expressed that vibrations due to the opening of the semilunar valves took part in the formation of the first sound (Cruveilhier,²² in 1841, and Ceradini,²³ in 1872).

Bamberger,²⁴ by simple auscultation, had concluded that during systole, when the first sound is heard, four sounds, which are superimposed and usually heard as two, are produced — namely, the tricuspid and mitral sounds, and those caused by distention of the pulmonary artery and aorta.

The pioneer records of the heart sounds taken by Einthoven and Geluk²⁵ showed a delay of about 0.06 second for the first sound recorded at the base of the heart, as compared with the same sound recorded at the apex, they therefore thought that the first sound at the base was due to the opening of the semilunar valves.

The part played by a vascular component in the genesis of the first heart sound was denied on the basis that this sound did not spread to any extent during the ejection phase of ventricular systole. This can no longer be doubted after phonocardiographic observations in animals (Wiggers and Dean²⁶) and in man (Schütz,²⁷ Weber²⁸ and Caeiro and Orías²⁹).

My own experience has shown that in human phonocardiograms obtained from the chest, it is extremely common to find that the first sound is composed of two principal groups of vibrations (Orías and Braun-Menéndez,²⁹ Orías³⁰ and Caeiro and Orías³¹). The records demonstrate clearly that one of these corresponds to the systolic isometric phase and the other to the ejection phase of ventricular systole. If the heart sounds are explored from different sites it is always possible to show this division appearing in at least one such area of auscultation either constantly or else during certain moments in the respiratory cycle (Caeiro and Orías³¹).

In fact, from the careful study of a large number of phonocardiographic tracings we are convinced

that vibrations of vascular origin form an important and as yet not sufficiently recognized proportion of the first sound as heard over the precordial area in normal conditions.

When, by reason of favorable circumstances the separation of the components of the first heart sound occurring during the isometric and the ejection phases of the ventricular systole is more accentuated, a true splitting of the sound may be recognized by auscultation and recorded by the phonocardiograph.

Auricular Component

The idea that vibrations of auricular origin contribute to the formation of the first heart sound has suffered many vicissitudes. The earliest records made of the first sound showed that this began 0.02 to 0.04 second before ventricular systole, which led some workers like Hürthle,³² Pawlinsky,³³ Weiss³⁴ and Roos³⁵ to believe that the initial vibrations were of auricular origin.

Later records showed that, although the earliest vibrations of the first sound sometimes preceded ventricular systole, they appeared *after* auricular systole (Battaerd³⁶ and Wiggers and Dean²⁶). This observation, together with the fact that when a separate clearly auricular sound existed, as in cases of gallop rhythm, these auricular vibrations preceded those of the first sound by a longer interval, led Wiggers³⁶ to deny the possibility of auricular participation in the formation of the normal first sound. In his opinion the small and slow initial vibrations that precede ventricular systole had not received an adequate explanation.

When more sensitive recording devices were used, especially in cases of delayed auriculoventricular conduction (incomplete, partial and complete auriculoventricular block) and in cases of transitory nodal rhythm it was shown that late manifestations of auricular activity contribute to the formation of the first heart sound.

Braun-Menéndez and Solari³⁷ by recording the heart sounds direct from the ventricular wall in dogs with auriculoventricular block, found that auricular contraction can produce sound vibrations persisting 0.20 second after the beginning of auricular systole and forming two groups of vibrations in the sound record. The first group of vibrations coincides with auricular contraction but the second group appears during full auricular diastole.

These facts satisfactorily meet Wiggers's objection that the auricular sound, when present, does not merge into the first sound. What happens is that when the first component of the auricular vibrations is sufficiently strong to be recorded, a clear auricular sound is observed, well separated from the first heart sound. In ordinary conditions it is the delayed components (second group) that contribute to, and so reinforce, the first sound.

ejection of blood from the ventricles into the arteries (vascular factor), and residual vibrations due to the preceding auricular contraction (auricular factor)

Before each one of these factors is analyzed it should be mentioned that sounds of the type observed in semiocluded arteries (Korotkow sounds), which may be produced by the action of the ventricular muscle on the coronary arteries, have also been suggested as an additional cause of the first heart sound (Laurell⁷)

It should also be emphasized that the factors mentioned above have not been listed in order of their relative importance. This will be considered below, for it varies according to the conditions and with the site of auscultation. However, almost everyone will agree that the valvular factor is the most important of all

Muscular Component

The existence of a muscular component in the first heart sound was debated for a whole century and is still a matter of dispute

In 1835-1840 the Committees appointed by the British Association for the Advancement of Science⁶ showed that a muscular factor was responsible for a great part of the first heart sound, for this could still be heard after closure of the auriculoventricular valves had been prevented by the introduction of a finger into the auriculoventricular orifice. Ludwig and Dogiel,⁸ in 1868, arrived at similar conclusions by placing ligatures in the auriculoventricular groove in dogs so as to prevent the free movement of the valves. They assumed that the sound still heard in such conditions was due to friction between muscle fibers at the beginning of systole. Yeo and Barrett,⁹ in 1885, Krehl,¹⁰ in 1889, Kasem-Beck,¹¹ in 1890, and Hess,¹² in 1920, repeated the experiments and confirmed the results of Ludwig and Dogiel

A dissident view appeared in 1933, when Dock¹³ interpreted his experiments, which followed the Ludwig and Dogiel pattern, as indicating that the first heart sound disappeared when the valvular motion was prevented. Subsequent experiments, however, along the same line have led Smith¹⁴ and Smith, Gilson and Kountz¹⁵ to the conclusion that elements initiated by the heart wall contribute to the production of the first sound

Eckstein¹⁷ approached the problem from another point of view. To ascertain whether or not myocardial tissue from a mammal's heart produces a sound during contraction, he removed the heart from a cat immediately after death and perfused the coronary vessels from a cannula placed in the aorta. While the heart continued to beat, the right coronary and the left circumflex branches were ligated. All the ventricular musculature was then cut away except a V-shaped strip surrounding the left ramus descendens. The weight of this strip averaged

about 6 gm. After ligation of the small vessels, the strip continued to beat, and with the occasional help of epinephrine the beat could be made forceful. When a receiver was sewed to such a strip of ventricular muscle devoid of valves, chordae tendineae and ventricular chambers, vibrations were still heard and recorded during contraction. The vibrations increased in amplitude and number after epinephrine, and this showed that they depended upon the vigor of contraction. That skeletal muscle produces a sound when it contracts has been known since the classic demonstration of Wollaston¹⁸ in 1810

The muscular factor may not be essential for the production of the first heart sound, but until further evidence is available it would be incautious to deny that muscular contraction per se is able to originate sound vibrations

Apart from the muscular sound discussed above, which is assumed to be due to the friction of the fibers against each other, it has been suggested that vibrations due to sudden tension of the ventricular walls also contribute to the formation of the first sound. This idea was put forward in 1895 by Geigel¹⁹ and shared by Goldscheider,²⁰ Frank and Hess²¹ and Hess.²² It has been expressed with slight variations by Frey,²³ Schütz²⁴ and Weber.²⁵

Current discussions of the causes of the heart sounds do not neglect the possibility of a muscular component in the first heart sound. In one of the latest reviews on the subject Rappaport and Sprague²⁶ state that "in spite of conflicting experimental evidence, it appears likely that contraction of the ventricle produces vibrations in the absence of valve closure. These (vibrations) contribute to the early part of the first sound"

On the clinical side, White,²⁷ in his well known textbook on diseases of the heart, says, "the first sound, loudest at the apex, is produced by closure of the mitral and tricuspid valves, plus an element of muscular contraction"

Valvular Component

Rouanet,²⁸ in 1832, seems to have been the first to regard the closure of the auriculoventricular valves as an important, or indeed the only, factor in the origin of the first heart sound. Obviously, of all the cardiac structures the valves seem the most likely to produce a sound by their closure. Said Rouanet: "They are thin, resistant, and inextensible, and pass suddenly from flaccidity to a state of very great tension," and this process explains the mechanism of production of the sound

Bayer,²⁹ in 1869, and Giese,³⁰ in 1871, showed that if, in a dead heart with artificial circulation, the auriculoventricular valves were suddenly placed in tension, a sound was produced

The changes in the characteristics of the heart sounds following valvular defects created by disease are further proof of the paramount importance

the auricles (Bridgman⁷⁴), and the friction of the auricle against neighboring structures

Once auricular contraction itself is finished, there is a possibility of residual vibrations in the above structures, and of new vibrations (Melik-Gulnasarian⁷⁵) owing to the movement of apposition of the auriculoventricular valves at the end of auricular contraction

All these factors probably combine in different proportions to produce the auricular sound, and account for its complexity in phonocardiographic records when it occurs separate from the first sound as in cases of auriculoventricular block (Braun-Menéndez and Solari⁷⁷)

The intensification of the auricular sound under special pathologic conditions implying myocardial damage, as in some cases of gallop rhythm, is further evidence of a muscular component in the genesis of the auricular sound

SUMMARY

There is experimental and clinical evidence pointing to four factors as contributing to the formation of the first heart sound: muscular contraction and tension of the ventricular walls at the onset of ventricular systole (muscular factor), closure of the auriculoventricular valves (valvular factor), movements and distention caused by the ejection of blood from the ventricles into the arteries (vascular factor), and residual vibrations due to the preceding auricular contraction

The second heart sound is due to vibrations produced by the closure of the semilunar valves on the valves themselves, in the walls of the arteries (pulmonary and aorta) and also in the blood column

The third heart sound is caused by vibrations of the ventricular walls due to their sudden distention by the inrush of blood from the auricles in the final moments of rapid ventricular filling

Muscular contraction and distention, passage of blood through the auriculoventricular orifices, distention of ventricular walls by the inrush of blood from the auricles and friction of the auricle against neighboring structures are the underlying factors accounting for the auricular sound

DISCUSSION

DR WILLIAM DOCK.* Dr Orias has given an excellent historical and critical review of the heart-sound problem to which I have nothing to add. However, I should like to do some subtraction and to recapitulate my heresies, already incorporated in two papers and presented to the sophomores each year until Dr DiPalma decided that it was not advisable to continue confusing the class in physical diagnosis.

Of the animal experiments the crucial one is that of Macleod and Cohn,⁷⁶ who inserted a piezoelectric device into dogs' hearts through the carotid artery or the jugular vein, to record the pressure synchronously with the electrocardiogram. Such a system records sound vibrations if they are intense and the records show clearly that the first sound is intense only at the auriculoventricular orifice, although vibrations are recorded, synchronous with the first sound and

with ejection, at the aortic orifice. The second sound is intense only at the aortic orifice. These observations seem to me to show that the dog's aorta, unlike its brachial and femoral arteries, does not give off a pistol-shot sound when the pulse wave enters it; they show that the first sound originates in the auriculoventricular, and the second in the semilunar valves. No vibrations of audible frequency were recorded from either the auricular or the ventricular walls with which the pick-up came in contact; the vibrations became attenuated rapidly a few centimeters away from their points of origin. In a continuous medium — air, water or steel — sound is attenuated according to the usual square of the distance formula, in discontinuous mediums — cork, rubber, air full of rain or snow, plasma full of red cells or muscle — sound is attenuated very quickly. Fibrous structures or crystalline structures such as bone and tendon, transmit sound fairly well. The aorta and pulmonary-artery walls are better sound conductors than the ventricles, and the aortic and pulmonary sounds are loudest at the points where the vessels come closest to the thoracic wall, not where the stethoscope is closest to the valves. The auriculoventricular valves insert into the annulus close to the great arteries, and the first sound is transmitted to and along these vessels. First sounds, greatly attenuated, also pass out to the chest wall through the ventricular muscle mass. With a stethoscope, one can hear the heart sounds of a mouse or a horse, when the heart is exposed and in the hand, even if the ear is placed fairly close; no heart sounds in dogs', calves' or horses' hearts are detected. If the muscle itself vibrated, the sound should be intense at the surface. A violin string plucked so as to set up vibrations as intense as those recorded at the auriculoventricular valve by Macleod and Cohn⁷⁶ when in contact with the recorder could be heard many meters away in air. It is not remarkable that the heart sounds — damped by blood and meat, lung and adipose tissue — were unheard so long, even after Harvey.

I agree with Dr Orias that the auricle, when it begins to contract, causes audible vibrations loudest next the esophagus, as shown by Taquini.⁷⁷ I think this sound is due to the sudden tensing of the valves of Vieussens and Thebesius, guarding the coronary venous orifices, which are just next to esophagus. This sound is never heard and rarely recorded from the surface of the body.

I agree that there is a pair of little clicks at the end of auricular systole, even when this occurs in mid-systole of the ventricles with the auriculoventricular valves firmly closed. This is believed to be due to the snapping back and forth of the interauricular septum as systole dies out first in one auricle and then in the other and venous blood surges in. During all the rest of auricular systole, there is dead silence — muscular contraction and interfibrillar friction occur, but what sound is produced is quenched before reaching the cavity or the surface of the auricle.

During ventricular systole there is dead silence except for a brief snap as intraventricular pressure begins to rise. Here, also, all sound due to motion and friction is quenched at its source. If the heart is empty, or if it contracts early in diastole before isometric relaxation has ended and ventricular filling begins, there is dead silence as one may observe in early ectopic beats. Here a contraction only a few thousandths of a second later in diastole, when the heart is filling but so empty that the weak beat fails to open the semilunar valves, causes a very loud first sound. In heart block, auricular fibrillation and ventricular tachycardia one regularly observes that beats occurring late in relation to phases of ventricular filling cause weak first sounds; those near the peak of a wave of filling cause loud sounds even when, as in ventricular tachycardia, the patient is pulseless and the second sound absent in the same beat.

Caudal to the third rib the first sound is almost purely valvular, but at the base vascular elements enter into it and the peak intensity may occur 0.02 to 0.04 second later than at the apex. First sounds at the base vary in intensity less than at the apex in the conditions named above. Rarely, the ear can detect splitting at the base in first sounds not split at the apex, so that the vascular element is distinct from the valvular element. Both elements arise in fibrous structures suddenly made taut by rising pressure, but even in anemia and aortic insufficiency the first sound at the base, in spite of the vigorous pulse wave and the closeness of the great vessels to the chest wall, is less intense than the apical first sound. Even at the base, the vascular vibrations may

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THE SECOND HEART SOUND

The origin of the second sound is much simpler than that of the first, and was well understood even by the very earliest investigators of the heart sounds.

The connection of the second heart sound with the closure of the semilunar valves was first precisely proposed and demonstrated by Rouanet²⁸ in 1932. He found that sudden stretching of an elastic membrane is always accompanied by a more or less distinct "snap," and on the basis of this simple experiment he could demonstrate what happens when the second sound is produced.

He inserted a vertical tube into the upper portion of an excised aorta, and into the other end, below the valves, another tube connected to a rubber balloon filled with water, which was compressed rhythmically. Each time that by decompression of the rubber balloon the reflux of the column of liquid was stopped by the semilunar valves, a sound could be heard if the ear was applied to the tube. Rouanet's explanation was adopted by Billing,⁴⁸ Carlisle⁴⁹ and Bouillaud.⁵⁰ His experiments were repeated and confirmed by the British Committee.

All the later anatomic, clinical and experimental observations have adduced new proofs in favor of the idea that the closure of the semilunar valves is the essential cause of the second sound, which is the acoustic expression of vibrations set up at this moment in the valves, in the walls of the artery and also in the blood column itself (Webster⁵¹).

In the ordinary conditions in which auscultation is made, the sounds originating in the aorta and the pulmonary artery, respectively, are heard as only one sound owing to summation. In cases of asynchronous closure of the semilunar valves, a reduplicated or split second sound is the result. The asynchronous closure of the semilunar valves as a cause of the split second sound was expressed without any objective basis before the phonocardiographic era but is now supported by experimental facts (Katz⁵² and Braun-Menéndez and Solari⁵³).

THE THIRD HEART SOUND

Many hypotheses have been proposed to explain the origin of the third sound. Here also, to a greater or lesser extent either the valves or the heart walls, or both, have been held responsible for the vibrations originating the sound.

Einthoven⁵⁴ thought that the third sound was caused by vibrations set up by sudden tension of the semilunar valves, but without definite statement of why this phenomenon should occur.

Gibson⁵⁵ and Hirschfelder⁵⁶ attributed the third sound to a transient and sudden closure of the auriculoventricular valves after the rapid filling of the ventricles. Gallavardin,⁵⁷ Benjamins⁵⁸ and Bridgman⁵⁹ supported this view. The study of venous pulse tracings optically recorded simul-

taneously with phonocardiograms eliminates, however, the possibility of any such valvular movement occurring at the moment at which the third sound is produced (Braun-Menéndez and Orías⁶⁰). Nor could Dean,⁶¹ by experiments in dogs, verify the existence of a valvular apposition at the time when the third sound is produced.

The third sound is produced in the final moments of the rapid ventricular filling as shown by its very constant relation with the last portion of the descending limb of the V wave (Ohm⁶² and Braun-Menéndez and Orías⁶⁰). From this observation the hypothesis has been advanced that the third heart sound is caused by vibrations of the ventricular walls that are due to their sudden distention by the inrush of blood from the auricles in the final moments of rapid ventricular filling. This conception was proposed by Ohm⁶² and has been supported by Frey,²³ Lian,⁶⁴ Gubergritz,⁶⁵ Melik-Gūlnasarian,⁶⁶ Leonhardt,⁶⁷ Schütz²⁴ and Braun-Menéndez and Orías.⁶⁰

By the term "ventricular walls" no distinction is implied between muscular and tendinous structures or valves. Furthermore, although the cause given above is stressed as the principal one, subsidiary factors should not necessarily be excluded.

The intensification of the third heart sound under special pathologic conditions implying myocardial damage as happens in some cases of gallop rhythm is further evidence of a muscular component in the genesis of the third sound.

Boyer⁶⁸ has presented experimental evidence to show that vibration of the ventricular wall produced in the quiescent heart by a very feeble impact gives rise to a sound very like the normal third sound in frequency, amplitude and duration.

On the clinical side, White²⁷ states "The third sound is probably the result of the vibration of the ventricular walls and auriculo-ventricular cusps caused by the inrush of blood every diastole."

CAUSES OF THE AURICULAR SOUND

One of the most important contributions made by the graphic method to the study of the acoustic manifestations of the heart's activity has been the recognition that, even in normal conditions, auricular contraction produces vibrations having the properties of sounds that are undoubtedly often heard at the surface of the chest in healthy persons, even under the ordinary conditions of auscultation.

During auricular activity various phenomena may produce a sound. Acoustic vibrations may be produced during auricular contraction by the muscular contraction itself as pointed out by Krehl,¹⁰ Roos,⁴⁴ Weber and Wirth,⁶⁹ Benjamins,⁵⁸ Reid,⁷⁰ Mond and Oppenheimer⁷¹ and Fogelson⁷², the tension of the auricular walls, the passage of blood through the valvular orifices (Kahn⁷³), the distention of ventricular walls by the inrush of blood from

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THE PHYSIOLOGIC COMPONENTS OF THE URINARY BLADDER*

Their Clinical Significance

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THE study of bladder function by cystometry has led to the conclusion that the bladder acts as a single unit. This was inevitable, since the cystometer registers the summation of changes in intravesical pressure resulting from detrusor contraction, without disclosing how such changes are brought about. Observation of the bladder during micturition under the fluoroscope, however, makes it quite clear that this concept is not entirely correct.

There are two functional units of the bladder that, by their synergism under normal circumstances, comprise the total detrusor function. These two units, which consist of the bladder base and of the dome, have a separate embryologic origin. The dome of the bladder develops from the cloaca, and is thus entodermal in origin, and the base is formed from the wolffian ducts and therefore stems from mesodermal tissue.¹ The base of the bladder is thicker than the dome, and this fact is of physiologic significance.² The function of the dome and of the base of the bladder can become separated under certain pathologic conditions, with the result that the dome will seriously hamper the action of the bladder base, and micturition then becomes inefficient. This pathologic state is more easily understood if the sequence of events in normal micturition in man is kept in mind.

In a previous paper³ it was pointed out that man has a distinct voluntary mechanism with which he starts and stops micturition. This mechanism uses the pubococcygeus, a large, paired, striated muscle with a somatic nerve supply, which, when relaxed at will, causes the region of the internal sphincter to drop downward. It is the displacement of the internal sphincter that precipitates the reflexes of micturition. The reflex for the ensuing detrusor contraction starts at the vesical neck and then propagates symmetrically and bilaterally to the base, to the sides and lastly to the dome of the bladder, so that at the beginning of micturition, after the downward tug on the internal sphincter, one can see quite clearly the contraction of the base followed by the rather marked contraction of the sides of the bladder. The bladder dome is thus raised, and at this moment the vertical diameter of the bladder becomes considerably greater, whereas the transverse diameter becomes smaller. At the moment micturition is deliberately stopped, the vesical neck becomes sharply elevated by the contraction of the levator ani muscles (including the pubococcygeus), the internal sphincter is shut, and first the base, then the sides and gradually the dome can be seen to relax, so that the vertical diameter of the bladder becomes smaller, and the transverse diameter larger (Fig 1). It will thus be clear that the bladder neck is the site at which the stimulus for the contraction of the detrusor originates, and from which the signal

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be less intense and record only as small late oscillations, with the peak of intensity synchronous at base and apex.

Dr Orías has properly stressed the contribution made by the vascular vibrations in determining the character of the first sound at the base. Most split first sounds, even at the base, are due to a synchrony of events on the two sides of the septum, not to separation of valvular and vascular elements. I am not aware of any clinical significance attached to detectable variations in the first sound as heard at the base, but such correlations may be noted in future by those who study these two factors at the bedside or in records of the sounds.

The auricular element recorded as blending into the first sound seems related to presystolic gallop. It might be called a belated, weak presystolic gallop, or fourth sound. These sounds, whether protodiastolic and due to early passive filling or late and caused by auricular systolic ejection, are not the result of tension in the ventricular walls. Apical records and border motion records made with the x-ray apparatus show that further filling follows the protodiastolic gallop or third sound, so that the ventricle could not be taut like a blown-up paper bag. Actually, the diastolic ventricle is never taut in that sense. If one prevents outflow in a dog's heart by clamping the aorta or inducing ventricular fibrillation, it balloons up to twice the volume normally reached in diastole, if the pericardium is then cut away it nearly doubles in volume again. In diastole the muscle is a jelly, capable of being drawn out to twice or thrice its usual diastolic column. If a Valsalva experiment is performed on a normal person with third sounds the heart shadow is far larger than during normal diastoles in which third sounds were recorded. The third and fourth sounds and the gallops occur when pressure between auricle and ventricle become equalized, the apex and lateral wall move basalward at this time, blood moves toward the auricle, and the valves may be drawn taut so quickly as to cause a sound louder than the first sound. If the patient has mitral-valve disease, and has a systolic murmur, the gallop, like the first sound, may be followed by a murmur, as Rydand has clearly demonstrated. Therefore, it is concluded that all sounds heard between the second sound and the true, or aortic-ventricular, first sound are due to tension of the valves at the end of a wave or rapid inflow.

To summarize, the apical first sound and all the third and fourth sounds and gallops are due to tension of the aortic-ventricular, and the second sound to tension of the semilunar valves. The basal first sound may contain elements, or rarely a distinct split sound, owing to the shock in the wall of the great arteries, usually, in man the pulse wave causes no sound in the aorta, and in dogs, in which brachial and femoral vessels have normally a pulse sound, the aorta has none, or a very feeble one. Most split first sounds are due to ventricular asynchrony.

The ventricular muscle is a good sound damper, as in the blood itself. The great vessels transmit sound fairly well.

The views expressed by Levine and Harvey⁷⁸ differ from those of White,⁷⁷ just as mine do from those of Dr Orías. Whether cardiologists live in the same town or in different hemispheres, clinical experience and honest careful study of their own and their colleagues' observations may lead them to diametrically opposed or deviant views. If this leads to further study, the profession has a future, when it leads one to believe his own or someone else's dogma, and stops experiment, the profession is dead.

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larger quantity of urine (Fig. 2) A bladder that has thus become quite large and overstretched loses much of its contractile power, and if micturition is possible at all, it will be accompanied by large residua. This loss of efficiency, however, may be only temporary, and the detrusor can recover much or all of its contractile power after the removal of an obstruction or after rehabilitation by means of drainage or other appropriate therapeutic measures in neurogenic vesical dysfunctions.

The shape of the bladder dome in obstructive conditions will vary, depending on the degree and the rate of development of the obstruction. The dome can hypertrophy evenly with the rest of the bladder, and the bladder configuration on the cystogram, except for the thickened bladder wall, may then resemble that of the normal organ. On the other hand, the bladder base may hypertrophy to twice the thickness of that of the dome so that with increasing failure of the detrusor to empty, the thin dome may balloon out considerably and assume a cystographic silhouette, as shown in Figure 3. In

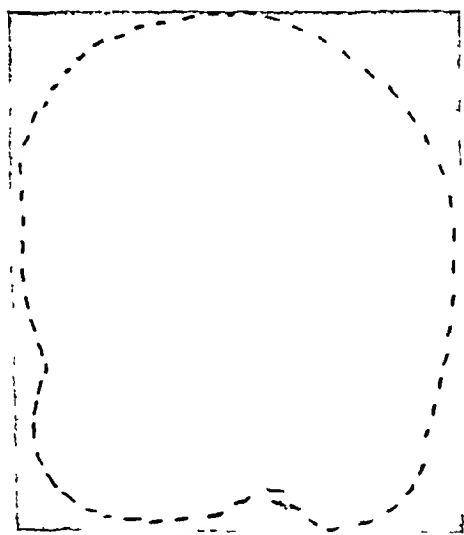


FIGURE 3 *Urinary Bladder in a Case of Benign Prostatic Hypertrophy*
Note the enormous dilatation of the dome

neurogenic vesical disturbances that lead to a big and overdistended bladder with large residua, the dome may become distended to enormous proportions (Fig. 4). When the dome has become markedly overdistended by whatever cause, it fails to assist the bladder base in the expulsion of urine. When the patient is still able to elicit a contraction wave from the bladder neck to the base upward, this wave tends to dissipate toward the dome, and the resulting slight increase in intravesical pressure may balloon out the dome somewhat further. It is under

such circumstances that the patient literally "voids into the dome of his bladder." In neurogenic vesical dysfunctions when the contraction of the detrusor has become enfeebled by overstretching, a large, dilated and therefore quite useless bladder dome may nullify the efforts of the detrusor to void. An overdistended noncontractile bladder dome therefore fails the detrusor in two respects. Being overdistended and noncontractile, it does not propagate or enhance the peristaltic wave, and by the same



FIGURE 4 *Urinary Bladder in a Tabetic Patient (Oblique View)*
Arrows point to the markedly dilated bladder dome

token, it wastes the increase in hydrostatic pressure that results from the contraction of the base and of the sides of the bladder, by directing much of that force upward toward the dome instead of downward toward the bladder neck.

To improve the efficiency of micturition under such circumstances it is necessary to correct these anatomic and physiologic changes of the bladder. In most cases this can be readily accomplished. If these changes, however, prove to be permanent, mere concentration on the vesical neck, or on means to stimulate the detrusor, will not restore adequate micturition. Under such circumstances improvement can be achieved if the useless bladder dome is excised. The resultant small bladder, which consists essentially of the bladder base and of its sides, can become a surprisingly efficient expulsive organ. In a previous communication,⁴ the beneficial results of such an operation in certain cases of prostatism was pointed out. Moreover, this procedure ought to be of value whenever the bladder dome irrevocably becomes a useless pouch. Resection of the bladder dome, however, is reserved only for patients in whom its permanent uselessness is demonstrated, and it ought not to be undertaken if its contractility can be restored by conservative means. The indication for this operation, therefore, must be carefully

for its relaxation spreads. The bladder base with its thicker musculature is therefore the primary expulsive motor force, and the dome facilitates the uninterrupted emptying of the bladder by contract-

in pathologic conditions. The study of bladder behavior in obstructive and in various neurologic dysfunctions was helpful in an interpretation of the events in the normal person.



FIGURE 1 Urinary Bladder in a Normal Male

A = bladder at rest (note the shape of the bladder base, and its relation to the symphysis pubis)

B = bladder during micturition (note the shape and the descent of the bladder base, the vertical diameter is now larger, and its horizontal diameter is smaller compared to its shape during the resting stage)

C = bladder immediately after deliberate cessation of micturition (The base and the dome have resumed the contour shown in A)

ing progressively and thus serving an important auxiliary function. It is the contraction of the dome that directs downward toward the internal sphincter

The thinner structure of the dome and its greater motility make it particularly suited to take up unusual pressure and volume changes of the bladder

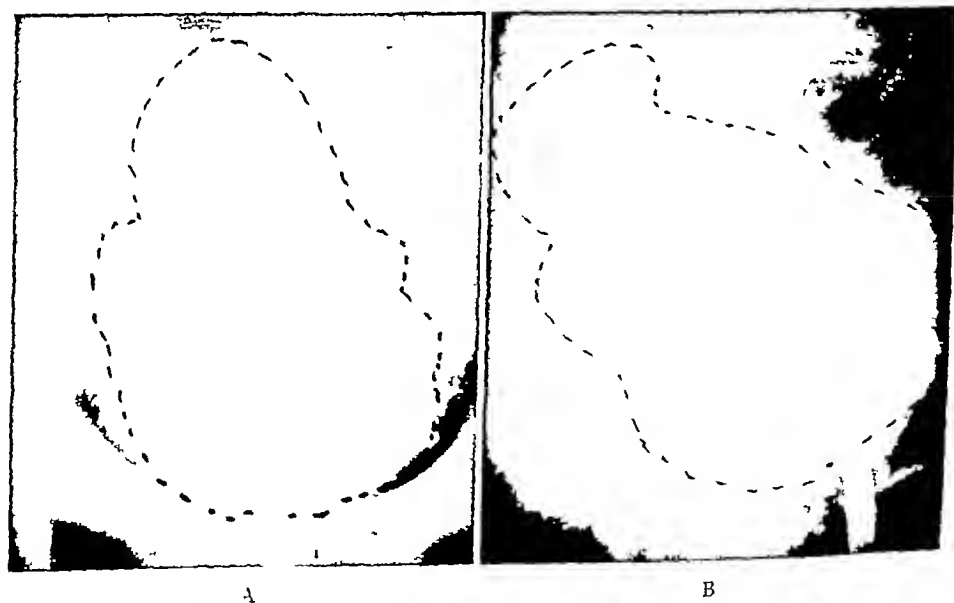


FIGURE 2 Urinary Bladder in a Case of Cancer of the Prostate

A = anteroposterior view

B = oblique view (note dilatation of the dome)

the increased hydrostatic pressure, resulting from the contraction of the base. The foregoing remarks are based on about 200 careful fluoroscopic observations of the function of the bladder in normal and

in certain obstructive or neurogenic vesical disturbances. Under such circumstances the dome and also the sides of the bladder can become markedly overdistended to accommodate the considerably

skin cancer are seen, and many more persons consult physicians for relatively insignificant growths on the skin in comparison with conditions twenty or twenty-five years ago

Thus, the five most common diagnoses include 1057 cases, or 50 per cent, the next ten diseases 1439, or 72 per cent, and fifteen diseases 1558, or 78 per cent. Many of these conditions are common to many ages and not necessarily restricted to this particular age group (see Table 2)

Not included in this group are conditions commonly occurring in older persons — that is, con-

rosacea, impetigo, pityriasis rosea, scabies, intertrigo, erythema induratum, molluscum contagiosum and pediculosis. As a matter of fact, they can occur at any age, but they are much more frequent below sixty. Rosacea was seen more often in women than in men (this condition is usually more apparent among patients thirty to fifty years of age). Erythema induratum, of course, is more frequent on the legs of female patients between ten and thirty, although 2 cases were seen in this group. Impetigo

TABLE 1 Age Group in Relation to Sex in 1000 Cases

AGE GROUP	MEN	WOMEN	TOTALS
35			
60-69	239	305	544
70-79	163	197	360
80-89	55	60	115
Over 90	1	2	3
Totals	456	564	1 000

ditions that would be found on a general examination in a large group, such as dry skin, atrophy, pigmented areas, graying of hair, thinning of hair, brittle nails and small tumors of various types. Many questions are asked on these subjects by patients being examined for other cutaneous disturbances.

In addition to this group, there was a group of relatively common dermatoses, which occurred less

TABLE 2 Most Common Skin Diseases

DISEASE	MEN	WOMEN	TOTALS
Senile keratosis	119 (5.9%)	169 (8.4%)	288 (14.4%)
Epithelioma	126 (6.3%)	160 (8.0%)	286 (14.3%)
Seborrheic keratosis	71 (3.5%)	105 (5.2%)	176 (8.8%)
Eczema	104 (5.2%)	72 (3.6%)	176 (8.8%)
Dermatitis contact	65 (3.2%)	66 (3.3%)	131 (6.5%)
Pruritus	44	54	98
Psoriasis	38	55	93
Seborrheic eczema	28	51	79
Dermatophytosis	39	26	65
Verrucae	12	35	47
Acne rosacea	7	30	37
Urticaria	6	16	22
Lichen planus	9	12	21
Herpes zoster	8	12	20
Syphilis	8	11	19

frequently among elderly patients. Table 3 demonstrates the diseases observed next in frequency. These are not particularly caused by increasing age but appear in the general population.

In Table 4 are listed relatively unusual dermatoses observed in this group. These usually occur at a somewhat younger age, but they have been noted in this series of older persons. Rare or unusual diseases were present in less than 5 per cent of this series.

More commonly observed in younger persons — that is, in those under sixty — are such diseases as

TABLE 3 Common Dermatoses Less Frequently Noted

CONDITION	No of CASES
Alopecia	17
Impetigo	16
Neurodermite	16
Hypertrophic	15
Mole	15
Dermatitis medicamentosa	13
Bacterial dermatitis	12
Mucocutaneous infections	12
Toxic erythema	12
Leukoplakia	12
Ulcer	11
Pityriasis rosea	10
Seborrhea capitis	10
Angioma	10

occurring in the older age group is often more obstinate than that seen in children. In certain cases it has responded very slowly, but such cases have been more responsive to penicillin than to some of the older antiseptic drugs previously used. Other diseases in this group were not seen very frequently.

It has been a surprise to us that there have not been more cases of certain diseases in these 2000 cases. There were only 2 cases of varicose ulcer and 13 cases of an eruption due to drugs, though it is possible that some of the cases of toxic erythema were drug eruptions. Leukoplakia would be thought

TABLE 4 Incidence of Relatively Rare Diseases

DISEASE	No of CASES
Pemphigus	11
Sarcoid	11
Multiple benign cystic epithelioma	9
Miliary lupoid	8
Melanotic sarcoma	7
Lymphoblastoma	6
Painful nodule of ear	6
Kaposi sarcoma	4
Lichen sclerosis et atrophica	5
Pseudopelade	3
Erythroplasia of Quevrat	3

to occur more often in this age group, and kraurosis vulvae, of which only 1 case was observed, is described much more frequently at this age. It is also surprising that more persons do not present themselves for graying or loss of hair. These items are expected perhaps as a part of growing old, although the advertisements of newspapers and magazines

established on an individual basis, and in conjunction with other measures calculated to remove obstruction and to enhance detrusor tonicity

SUMMARY

The urinary bladder in man is made up of two integrated functional units, which consist of the bladder base and dome. These two units have a separate embryologic basis and differ in their physiologic function. The bladder base is the primary motor force in micturition, and the bladder dome acts in an auxiliary manner. Under certain pathologic conditions, the bladder dome can become

permanently overdistended and noncontractile. When this occurs, the dome interferes with the expulsive efforts of the base, and micturition becomes inefficient. Excision of the useless dome remarkably increases detrusor efficiency.

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GERIATRIC DERMATOSES*

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DISEASES of the aged are becoming increasingly important in the economic, social and medical life of the country. Whereas in 1910 only 4.3 per cent of the population were sixty-five or over, in 1950, 7.9 per cent of the population will be in this age group, and in another ten years, 10 per cent of the population will have reached this age. Thus, the diseases of this group require and will continue to require greater attention on the part of all physicians. In addition, the infirmities accompanying the aging process are apt to be slower in responding to treatment or to become more chronic so that more individual medical attention is required.

From the medical standpoint the diseases of this age group affect many systems of the body, and it is seldom that only one system is involved. The skin and its accessories participate in the changes of advancing years, but little attention has been paid to the part that these cutaneous disturbances may play in the life of the person affected. Many of these manifestations on the skin persist because of some other disease or condition, such as a circulatory abnormality, nutritional deficiencies, lack of proper care, failure to realize implications of a relatively insidious onset and often a real neglect. Thus, the disturbances on the skin must be considered in the light not only of the age of the patient and his general medical condition but also of various other factors.

Since comparatively little attention has been given specifically to the skin disturbances of this age group it seemed of interest to review the records of 2000 private patients over sixty years of age for the pur-

pose of determining the diagnosis of their diseases and discussing them.

This survey was made several years ago and included many records of the late Dr. Arthur M. Greenwood, as well as our own records. Of these 2000 cases, 785 (40 per cent) were in men, and 1215 (60 per cent) in women. The proportion of women to men in these figures is much higher than that in Massachusetts or in the country at large, although it is a fact that after sixty years of age the proportion of women to men is somewhat greater. We do not believe that these figures indicate that women have a higher percentage of disease in this age group, but rather that women are more apt to seek the advice of a physician.

So far as ages are concerned, 1145 patients (57.25 per cent) were between sixty and sixty-nine, 677 (33.85 per cent) between seventy and seventy-nine, 170 (8.5 per cent) between eighty and eighty-nine, and 8 (0.4 per cent) over ninety years of age. A characteristic distribution according to age and sex among 1000 patients is shown in Table 1.

Table 2 presents data concerning the most common skin diseases found in this group.

Although these figures do not indicate the frequency with which the diagnoses would be observed in patients given a general examination in this age group, it will be seen that senile keratosis (the precursor of epithelioma), epithelioma, seborrheic keratosis, eczema and contact dermatitis were the most common conditions for which older patients consulted a dermatologist, or at least the most common conditions found on examination by a dermatologist. One wonders if the relatively large number of cases in the first three groups was due mainly to campaigns against cancer carried out over a period of years. Certainly, far fewer neglected cases of

*Presented at The New Orleans Graduate Medical Assembly, March 8, 1949.

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ing down the scaling and crusting over a considerable period in the very superficial type. If infiltration developed, or actual ulceration, it was probable that a malignant change had already developed, and the lesions were treated as basal-cell epithelioma.

SEBORRHEIC KERATOSIS

Seborrheic keratoses, sometimes spoken of as senile flat wart or verruca seborrheica, were in general quite different. They were usually on covered parts of the body, such as the upper back, over the shoulders and over the chest. They were found, however, on the face, hands and abdomen. In general, these were sharply outlined, oval, slightly elevated, usually slightly pigmented and perhaps slightly greasy lesions. In certain persons there was often difficulty in distinguishing some of these lesions from the senile keratoses, but in general a distinction could be made. A definite hereditary factor was indicated by the fact that the lesions were seen in certain members of a family over two or three generations, or that such a history could be obtained.

In view of the fact that they seldom became malignant their removal was not necessary except for cosmetic reasons. They were destroyed in various ways as seemed necessary.

ECZEMA

Eczema and dermatitis are, of course, the most common diseases of any age group. It is a question whether there should be much distinction between cases of eczema and those of dermatitis. Both terms refer to an inflammatory reaction in the skin. The term "eczema," perhaps, will not disappear, but its use has decreased much in dermatology, and the term "dermatitis," either acute, subacute or chronic, has become more widely employed for simple inflammations of the skin, whether of external or internal origin. In this older age group the term eczema has been used for cases of inflammation of the skin that were not definitely due to an external contact, and in many cases no single factor could be assigned as a cause. The skin disturbance seemed more intractable than in younger persons, a fact that was particularly true when the lower legs were affected. We believed that there was often a circulatory factor, although not always associated with obvious varicosities. Many of these cases started with a pruritus or perhaps a mild dermatitis, with exaggeration thereafter by the trauma of scratching or rubbing, perhaps by low-grade secondary infection, sensitization to some therapeutic agent and stasis — that is, being on the feet too much for the circulatory system of the particular patient and so forth. Etiologic factors were often multiple. There were found in the cases in this group various degrees of itching and discomfort, and varying amounts of redness, swelling, excoriations, scaling, crusting, infiltration, pigmentation and so forth. Much patience was often required to obtain an account of the onset and course of the disease from

these older people and their relatives, and to ascertain something of earlier treatments and the results of such therapy.

Recently Guy et al* discussed geriatric nutritional eczema in patients past middle life with an eruption of the lower legs associated with varying degrees of edema. Hypoproteinemia was a main factor, and edema was abolished when an adequate supply of protein was given. These patients were usually amenable to a six-point plan of treatment: adequate mastication, a diet rich in proteins, administration of protein hydrolysates, concentrates and vitamins, correction of hypochromatic anemia, dilute hydrochloric acid with meals, and local care in keeping with the status of the inflammatory process. The additional factor of possible focal infection was brought out in the discussion of this report.

Treatment often had to be individualized, and careful, preferably written, directions given for the regime that was prescribed. Much time was often consumed in the details of treatment of acute, subacute and chronic types. Suffice it to say that soothing combinations, such as a modified calamine lotion and a zinc oxide or calamine, starch and vaseline ointment were usually prescribed at first. With much oozing and much redness and swelling, boric acid or weak potassium permanganate compresses were often well tolerated. Occasionally, an oil as a cleansing agent seemed preferable. In many cases in which the leg was affected it was essential that the patient keep off his feet, or wear a linen-mesh bandage properly applied.

A rather high percentage of these cases of contact dermatitis among older persons seemed to be associated with the soap that was used. There were a few cases due to nail polish, a few to plants, a few to nickel, and a few to paint solvent, and there were 1 or 2 cases of a large number of different agents with which the patient had been in contact. A great many of these cases involved the hands. Detection of the offending agent and its elimination were important for therapy but often difficult to achieve.

PRURITUS

Pruritus was a very troublesome symptom. It is hardly necessary to emphasize the disastrous effect that a mild but persistent itch can have on the life and general condition of the older patient. And a severe pruritus, if unrelieved, will prevent the sleep the patient needs, interfere with appetite and general nutrition, depress him mentally and in general greatly affect the general health.

About 50 per cent of the cases were of the so-called senile type, with very few or no demonstrable skin lesions except for the excoriations produced in an attempt to relieve the itching by scratching. Of the remainder, localized perianal and vulval itching

*Guy, W. H., et al. Geriatric nutritional edema. *Arch. Dermat. & Syph.* 57:822-827, 1948.

may lure them when the dermatologists' pessimistic prognoses fail

Before the more common dermatoses noted in this group are discussed it is hardly necessary to emphasize that senile cutaneous changes do not develop at any particular age. The onset of such changes is just as variable as the beginning of senile changes in the ear, eye, joints and arteries, and the rate of alteration varies greatly in different persons. In the general examination of older patients the physician finds that as the years pass the subcutaneous fat is lessened, the skin becomes less elastic and thinner, more wrinkling develops, the color may become grayish or yellowish, perhaps with pigmented or depigmented areas, and there may be a variable amount of dryness and scaling, especially in cold weather. There is also the appearance of gray and white hair, as well as the thinning and possibly entire lack of hair on the vertex in men. In addition, the physician will find in many older people hyperpigmented areas, especially on exposed surfaces, with varying degrees of pigmentation, including depigmentation, small capillary tumors or angiomas, small pedunculated fibromas, small verrucae, keratoses and so forth, many of which have been present so long or have developed so gradually that they are accepted by the patient as a part of the aging process.

EPITHELIOMA

In this series it will be noted that skin cancer, or epithelioma, and its precursor, keratosis senilis, constitute the largest group of cases observed in this series—574, or 28.7 per cent of the total number of cases. In fact, in many cases epithelioma and keratoses of both types were found in the same person. The number of women with epithelioma was very much larger than the number of men. In one of our groups the number of women with epitheliomas was almost twice that of the men. In that same series the proportion of brunettes was very much larger than blondes. The nose and cheeks accounted for more than half the cases. Cancer of the skin was found in two clinical types. The milder type—the basal-cell epithelioma—was usually a pearly nodule or ulcer with a pearly border and central crust, though there was considerable variation in its appearance. The more serious type—the squamous-cell epithelioma, which was less frequent—developed more rapidly, had more ulceration, was a deeper process and tended to metastasize.

When seen early these lesions were treated very satisfactorily with x-rays or radium, occasionally, desiccation was used, or excision advised. The dose of radium or x-rays was varied with the size and depth of the individual lesion, but an adequate border about the lesion was included and the dosage was sufficient to produce necrosis of the area. Excision must be wide enough to remove any possible extension of the tumor mass, and desiccation

in the same way should include enough area to eradicate any fingerlike processes from the main tumor.

Cancer is a serious disease, but cancer limited to the skin does not have the relatively serious prognosis of cancer of the other organs. This abnormal process on the skin is external and visible or palpable, or both, and if treated properly and early in its development can be absolutely eradicated. In fact, it can be stated that mortality from skin cancer can be absolutely prevented by the co-operation of the patient in presenting himself for diagnosis at the earliest possible moment and by the co-operation of the physician in early diagnosis and complete eradication. However, if one considers in this group cancer on the lip and tongue and oral cavity, the seriousness of prognosis is greatly increased, and early diagnosis is of far greater importance.

The campaign against cancer has been most helpful as far as skin cancer is concerned, but perhaps more emphasis should be placed on this form of cancer. Much disfigurement and perhaps even death might be prevented by any form of lay campaign by medical or public-health groups emphasizing the desirability of reporting for examination of even minor, localized changes in the skin as the patient becomes older. In any such campaign at the same time physicians need to be reminded of possible malignant changes developing in apparently insignificant lesions in persons over sixty years of age. Of course, basal-cell carcinoma has been seen in the teens and twenties, but in the older age group it is much more frequent. The tumor clinics established in many hospitals, with a surgeon, radiologist and dermatologist in attendance, have been important factors in many communities in education about cancer in this age group, as well as furnishing diagnostic and therapeutic centers.

SENILE KERATOSIS

As with epithelioma, the figures in this series indicate that these keratoses appear more frequently in women than in men. Senile keratoses are real precancerous lesions. They occur chiefly on exposed surfaces, and they are seen more commonly in persons much exposed to the sun and wind and in those of blond or "sandy" complexion. They may occur anywhere on the face, more frequently (in this series) on the forehead, upper cheeks, nose, ears, sides of the neck and dorsal surfaces of the hand. They are usually red, slightly scaly and quite sharply outlined, often with slightly or even tightly adherent crusts, which are sometimes dark, dry and often hard. These crusts frequently come off but soon re-form.

These lesions were destroyed by desiccation, radium or x-rays, or by trichloroacetic acid adequately applied. A mild salicylic and sulfur ointment, 2 to 4 per cent of each in white vaseline or cold cream, was often helpful in removing or keep-

Women had a higher incidence of epithelioma and keratosis, as well as other diseases, and men a higher proportion of inflammatory diseases, such as eczema and contact dermatitis and fungous infection.

Relatively few unusual diseases were noted.

It is important that minor changes in the skin be examined early to prevent later extensive involve-

ment, and that apparently insignificant growths be examined to determine if malignant lesions exist and to provide adequate therapy. The relief of itching and discomfort is quite important.

In older patients it is especially necessary that the patient as a whole, and not merely his cutaneous disturbance, be considered and treated.

REACTIONS FROM THE USE OF BENZODIOXANE (933 F) IN DIAGNOSIS OF PHEOCHROMOCYTOMA*

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PHEOCHROMOCYTOMA is a known cause of hypertension that is being more frequently diagnosed.¹ This tumor produces epinephrine or an epinephrine-like substance that is responsible for the observed increase in blood pressure. Pharmacologically the dioxane group of drugs (883 F, 933 F, 1164 F and others) prevent or reverse the hypertension produced by epinephrine in animal experiments.^{2,3} The compounds 883 F and 933 F do not have any significant effect on the blood pressure of dogs or rats with renal hypertension.^{4,5} Thus, the benzodioxane group of drugs would be expected to prevent the effects of circulating epinephrine produced by a pheochromocytoma, and thus to reduce blood pressure, but would be without effect in the patient with other forms of hypertension. Recently, a test for hypertension due to circulating epinephrine has been devised, on the basis of the adrenolytic effect of benzodioxane derivatives.⁶

The use of such drugs to block the effects of epinephrine will provide a more specific test in the diagnosis of pheochromocytoma. However, such agents as the benzodioxane derivatives can produce many side reactions that have not been sufficiently emphasized. The present paper reports the occurrence of severe side reactions resulting from the injection of a benzodioxane derivative in 2 patients with suspected pheochromocytomas.

METHOD OF ADMINISTRATION

The benzodioxane derivative used was 933 F (piperidino-methyl-benzodioxane). It was administered by the technic and in the dose utilized by Goldenberg, Snyder and Aranow.⁶ The patient received an intravenous infusion of 5 per cent glucose, and with the infusion running control determinations of blood pressure were taken each minute for approximately twenty minutes. When the patient was adjusted to this procedure 933 F

was injected into the infusion tubing for two or three minutes in a dose of 10 mg. per square meter of surface area.

CASE REPORTS

CASE 1 A 51-year-old woman was admitted to the hospital complaining of severe headaches, blurred vision, nerv-

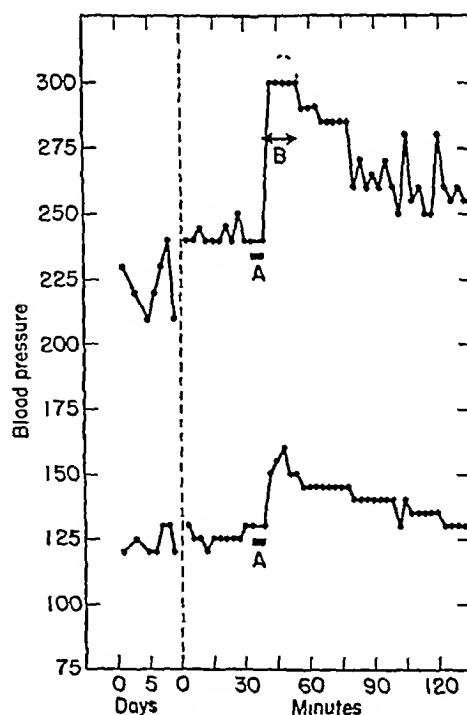


FIGURE 1 Zero Time (Control Infusion Started)
Injection of 933 F at A. Complaint of nausea and headache at B.

ousness and weight loss. These symptoms had begun 3 years previously, with anorexia and headache. This was followed by a gradual onset of fatigability, attacks of dizziness, nervousness and palpitation. The headaches became worse, and 2 months before admission she complained of blurred vision and yellow spots before the eyes. The weight loss during this period was 36 pounds.

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formed the largest group. In many cases both areas were involved. Only 6 per cent of these cases were of diabetic origin. The diagnosis of pruritus particularly a generalized pruritus, called for a careful detailed examination to prove conclusively that there was no general causal factor. Such itching is, of course, associated with diabetes not infrequently, the lesions of the lymphoblastoma group, liver conditions and other diseases. In the same way, localized pruritus called for investigation, both for a local causal factor and for general factors. In the northern part of the country numerous cases of pruritus of the generalized type appear in older persons with the onset of cold weather and clear up in the spring—the “winter itch,” or pruritus hiemalis. The neurogenic factor was a more difficult one to evaluate in both the general and the local type, but in cases of perianal, vulval and scrotal pruritus in which only the results of rubbing and scratching were apparent, with no other lesions to account for the itching, a neurogenic factor was given serious consideration.

Treatment of these cases was often difficult. It is imperative that all possible causal factors found on general examination be eliminated so far as practically possible. Frequently, in the general type, the kind of soap seemed important, and the use of a so-called superfatted soap or of less soap, or perhaps no soap at all, in bathing, followed by some mild emollient, often provided considerable relief. The treatment of the localized pruritic areas in older patients is often a severe test of the physician's therapeutic skill. Phenol is still the best single antipruritic agent, and menthol and camphor can be useful in treatment, but careful observation is required to be sure that these agents do not act as sensitizers. Whether some of the new antihistaminic agents will prove useful in these cases still remains to be proved. The itching was often an individual problem and can hardly be discussed in general without an individual case for consideration. Mild sedation was a helpful ally in many cases but was discontinued as soon as possible. Fractional x-ray therapy was used in carefully selected cases. It is to be deprecated that x-ray therapy has been employed to such a degree that numerous cases of atrophy and telangiectasia, with the resulting sequelae, appeared as the result of such radiation of localized pruritus. It is essential that a limit be set upon the amount of treatment to be given the individual area, and when that limit is reached the patient should be informed that his particular quota has been reached and it is inadvisable to continue further with such treatment. It is, of course, essential that every attempt be made to maintain accuracy of dosage if radiation is prescribed.

DISCUSSION

Space does not permit the discussion of the other diseases noted in this series. In addition to the

diseases mentioned above there were many diseases in which only 1 to 4 cases have been listed. Thus, there are many diseases of the skin with which the older patient can be afflicted and for which he will seek relief.

In the care of these patients it is well to remember that the older skin is drier and that less soap or perhaps a so-called super-fatted soap is frequently helpful. In addition, in colder weather the use of a thin oil or grease often gives considerable relief. Additional protection from cold weather gives relief in many cases, although wool seems to have an effect of producing itching in some.

In many older persons there was need to compromise with the usual directions given for the care of some skin diseases. There was the need to compromise with a strict diet if such diet seemed as if it would interfere with the daily routine of life that had been carried on over many years. Although it was essential to give very careful directions, perhaps in writing, it was necessary to compromise on some of the details to avoid complicating the life of the patient or family too much. Some of these patients were extremely meticulous, others very carefree, and others very forgetful, so that such directions varied with the individual patient. Relief of itching, especially of generalized itching, was of prime importance in many of these cases. Much consideration had to be given to procedures that were *essential*—treatment of skin cancer, remaining off the feet and so forth—as compared with measures not absolutely essential. In many cases improvement or relief was brought about by unusual methods or unacceptable proprietary applications, and it often seemed best to go along with such methods for a while without too sudden changes, with a gradual shift to methods and agents that should really have done better for the patient. It was often a difficult matter to decide whether to accept and go along with preconceived ideas or to attempt to alter them to a more generally accepted method. In other words, it was often especially necessary to treat the patient with the disease and in relation to his other diseases and not simply the cutaneous disease with which he was afflicted.

SUMMARY

The case records of 2000 patients over sixty years of age with diseases of the skin are reviewed.

The most common diseases observed in this age group are discussed.

Fifty per cent of these patients received a diagnosis of one of five diseases,—senile keratosis, epithelioma, seborrheic keratosis, eczema or contact dermatitis,—and in 79 per cent the diagnosis was one of fifteen other diseases.

Senile keratosis and epithelioma—that is, premalignant and malignant disease—accounted for 28 per cent of the cases.

and tachycardia⁷ The hypertension and tachycardia caused by 933 F is a sympathomimetic effect that is not seen in the anesthetized animal The effect of epinephrine on the heart rate is not abolished by 933 F, on the contrary the drug increases the tachycardia produced by epinephrine Thus, side effects of this nature may be expected in some patients when 933 F and related compounds are used

The effect of the benzodioxane derivatives in lowering the blood pressure of patients with pheochromocytoma⁶ has been confirmed⁸ In such studies it was found that the usual response produced by 933 F in patients with essential hypertension was an increase in blood pressure⁶ Normal subjects also showed a rise in blood pressure after injections of 933 F, but less so in comparison with patients with essential hypertension Other side reactions were noted, such as flushing, palpitation, nervousness, cold and clammy extremities, hyperpnea, mild headache, fright, sighing and dizziness These reactions were seen chiefly when the injection of 933 F was made in thirty seconds and were noted much less with an injection time of two minutes

In the 2 cases reported above, 933 F produced a marked rise in both systolic and diastolic blood pressure That this is a central effect of the 933 F is seen by the simultaneous increase in pulse rate Other side effects were nausea, headache, dizziness and flushing, and 1 patient complained of severe precordial pain

The central-nervous-system stimulation caused by 933 F, as reflected in the marked increase in blood pressure and the tachycardia, is a dangerous side reaction, and is an inherent property of such

compounds that apparently becomes more manifest in patients with hypertension that is not due to pheochromocytomas A different type of adrenolytic drug, dibenamine hydrochloride, that may also stimulate the central nervous system has recently been reported The use of dibenamine in the diagnosis of a case of pheochromocytoma has recently been described⁹

SUMMARY

An adrenolytic drug, 933 F (2-piperidino-methyl-1, 4 benzodioxane), was administered to 2 patients with suspected pheochromocytomas

The injection of 933 F produced an immediate and marked rise in systolic and diastolic blood pressure, and 1 patient complained of severe precordial pain The possible toxic effects of such compounds are discussed

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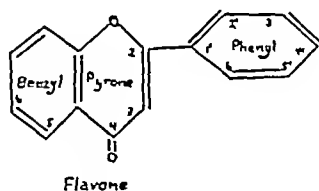
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- 2 Fournieu E. and Buvet D. Recherches sur l'action sympathicolytique d'un nouveau dérivé de dioxane *Arch. internat de pharmacodyn. et de therap* 46 178-191 1933
- 3 de Vrieschhuwer G. Influence d'un nouveau dérivé de la dioxane sur les réflexes vasomoteurs et sur l'hypertension adrénaïque et nicotinique *Compt rend Soc de biol* 115 1247-1249 1934
- 4 Bing R. J. and Thomas C. B. Effects of two dioxane derivatives 883 and 933 F on normal dogs and on animals with neurogenic and renal hypertension *J Pharmacol & Exper Therap* 83 21-39 1945
- 5 Sapirstein L. A. and Reed R. K. Effects of Fournieu 883 and Fournieu 933 on late renal hypertension in rat. *Proc Soc Exper Biol & Med* 57 135 1944
- 6 Goldenberg M. Snyder C. H. and Aronow H. Jr. New test for hypertension due to circulating epinephrine *J A M A* 135 971 976 1947
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- 8 Cahill G. F. Pheochromocytomas *J A M A* 138 180-186 1948
- 9 Spear H. C. and Griswold D. Use of dibenamine in pheochromocytoma report of case *New Eng J Med* 239 736-739 1948

DEFINITION

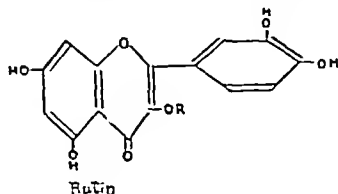
Until recently, the only abnormality detectable in laboratory animals deficient in vitamin P was an increased capillary fragility, and substances that could correct this abnormality were described as having vitamin P activity. The term has acquired a broader meaning and is used to describe agents that increase the strength of capillaries of normal animals. Because of the unreliability of tests of capillary strength, other procedures have been suggested to demonstrate vitamin P activity. Thus, pulmonary hemorrhages have been produced in mice by sudden reduction in atmospheric pressure. It has been claimed by some²¹ but denied by others²² that vitamin P reduces the severity of this type of hemorrhage. Other suggested bases for biologic assay are the reduction in bleeding time in normal guinea pigs²³ and the increased resistance of erythrocytes to hypotonic saline solution,²⁴ both of which are effected by vitamin P. It is obvious, then, that the term vitamin P has exceeded the usual limits that one associates with the word "vitamin."

CHEMISTRY

The many types of vitamin P have a similar structure. They may all be regarded as derivatives of flavone proper (phenyl gamma benzo pyrone) or its variations.^{25 26}



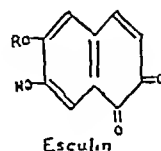
When the double bond between carbon atoms 2 and 3 is saturated, the compounds are called flavonones, examples of which are hesperidin and eriodictin (eriodictol). When a hydroxyl group is attached to the third carbon atom, the structure is known as a flavonol, of which rutin is representative. Derivatives of these three variants of the flavone nucleus are collectively referred to as flavones. Rutin, for example, is the rhamnoglucoside of 3, 5, 7, 3', 4' pentahydroxy flavone.



Flavones

The flavones are a group of yellow, plant dye-stuffs that are widely distributed in nature, being

found in citrus fruits, tobacco plants and buckwheat. The last is the present commercial source of rutin. The existence of the flavones was known long before their vitamin P activity was appreciated. Hesperidin, for example, was discovered in 1828.² More recently isolated types of vitamin P are the flavins²⁷ and coumarins,²⁸ represented by *d*-epicatechin and esculin respectively. In the former, the ketone group on the fourth carbon atom of the flavone nucleus is reduced, and the double bond between the second and third carbon atoms is saturated. The coumarins show the greatest divergence from the flavone nucleus. The phenyl ring is lacking, the pyrone ring is reduced, a double bond lies between the first and second carbon atoms, and ketone groups are attached to the third and fourth carbon atoms.



D-epicatechin and esculin are among the most potent types of vitamin P, having an activity at least five hundred times that of citrin. Catechins are extracted from vegetables and kola nuts, and esculin is derived from chestnuts.

IDENTIFICATION OF VITAMIN P COMPOUNDS

Spectrographic analysis is the only certain method for the identification of individual vitamin P compounds. Various colorimetric procedures are available but they are all group specific.^{27 29 30} Since not all flavones or catechins are endowed with vitamin P activity, the results of colorimetric procedures need not be synonymous with vitamin activity.

METABOLISM

Very little is known of the fate of vitamin P after its ingestion. The little information available deals only with the soluble type of compound. As yet no one has traced the pathway of insoluble compounds like rutin given by mouth. When soluble compounds are injected parenterally, a variable portion may be recovered in the urine and bile for a period extending over several hours or days.^{31 32} The amount excreted depends, in part, on the previous body store of vitamin P. Other factors that govern excretion, the fate of the unrecovered fractions and the intermediary metabolism in the body have all to be worked out.

PHARMACOLOGY OF VITAMIN P

Different types of vitamin P have different pharmacologic properties.³³ Some, like eriodictol, are inert when injected intravenously. Others like

MEDICAL PROGRESS

THE BIOCHEMISTRY AND CLINICAL APPLICATION OF VITAMIN P*

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THE term vitamin P was proposed by Armentano and his co-workers¹ to denote a group of compounds distinct from ascorbic acid that maintained the physical strength of capillaries. This concept grew out of investigations to determine why crude sources of vitamin C controlled hemorrhages in vascular purpura whereas purified ascorbic acid was ineffective. From the ascorbic-acid-free residue of the mother substance, a faintly yellow crystalline material, which was found to exert the so-called vitamin P activity, was extracted. Because of its derivation from citrus fruits, this active powder was called citrin. Various analyses revealed that citrin was a mixture of different flavones, and several of these were subsequently isolated.² Their potency has been the subject of considerable debate. Opinions also differ concerning whether these compounds actually function as vitamins. The original claims^{3, 4} that vitamin P prolonged the lives and reduced the severity of the symptoms of scorbutic guinea pigs failed to stand up to independent investigation,^{5, 6} and even Szent-Gyorgyi⁷ could not confirm the initial results.

Early investigations were hampered by the difficulty of preparing a diet completely free of flavones. In addition, because of the similar natural distribution of flavones and ascorbic acid, diets that excluded sources of flavones were also deficient in vitamin C. Animals maintained on such regimes developed scurvy, which masked possible effects of vitamin P deficiency. It remained for Zacho⁸ to achieve a pure vitamin P deficiency state in his animals by adding pure ascorbic acid to their flavone-free diet. The only abnormality that developed in such animals was a capillary weakness, which responded specifically to vitamin P. This claim has been well substantiated.^{9, 10} Scarborough^{11, 12} has described a vitamin P deficiency in human beings characterized by capillary weakness, spontaneous perifollicular hemorrhages and rheumatic pains in the legs and shoulders. Again, a specific, rapid response to vitamin P was claimed, whereas ascorbic acid was ineffective. Although Scarborough's work seemed to be well controlled, his findings could not be con-

firmed by Lazarus and his co-workers,¹³ who maintained that neither vitamin P nor ascorbic acid remedied the capillary weakness in scurvy. From this welter of conflicting evidence, it is impossible to arrive at any definite conclusions. Possibly, the use of injectable preparations might lead to more uniform results.

Regardless of their acceptance as vitamins, the flavones have attained an important position in clinical medicine because they appear to exert a nonspecific, stabilizing effect on capillaries. This applies to a wide variety of pathologic conditions in which capillary defects are present. In addition, as pointed out below, evidence that vitamin P stabilizes ground substance opens new avenues of investigation into the relation between vitamin P and the numerous diseases to which ground substance falls prey.

When capillaries that are subjected to physical stresses rupture excessively and form petechiae, they are said to display increased fragility or decreased resistance. The physical stresses are either an increased intracapillary pressure obtained by the application of a blood-pressure cuff to the upper arm or a negative external pressure obtained by the application of a suction cup to the skin.

These tests have recently been reviewed in detail.¹⁴ The numerous modifications to which they have been subjected clearly indicates that they leave much to be desired. There is no correlation between positive and negative pressure. When performed at the same time the tests may yield entirely divergent results.¹⁵ Influences on capillary resistance due to age,¹⁵ sex,¹⁶ season, time of day, emotions,¹⁷ trauma¹⁸ and hemorrhage, render the interpretation of these tests most difficult. The confusion has been compounded by the failure of many investigators to heed the warning¹⁹ that tests repeated at intervals of less than three weeks may yield false-negative results.

The term "increased capillary permeability" is also used loosely to indicate a weakness of capillary walls. Capillary permeability is gauged by the extent of transudation following venous stasis¹ or by the degree and rate of streamer formation following the intradermal injection of the dye patent blue.²⁰ In contrast to the fragility measurements, the permeability tests have had a limited application

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increase the strength of capillaries,⁴⁷ and the parathyroid hormone to increase the resistance of the connective tissue.⁴⁸ Thus, vitamin P is visualized as regulating capillary resistance by an endocrine mechanism based on the ability of epinephrine to mobilize the pituitary gland and its target glands. It is not yet known whether adrenochromes can emulate this action of epinephrine on the endocrine system. Since adrenochromes are devoid of most of the properties that limit the administration of epinephrine, such information might be of considerable practical as well as academic interest.

The Direct-Action Theory

A theory commendable for its simplicity is that of Lenaz and Alborn.⁴⁹ It was based on their finding that blocks of agar in citrin solution absorbed considerably less fluid than those in a control medium. The results were interpreted according to the postulate of Gellhorn that colloid hydrophilia was a function of colloid permeability. Since citrin decreased the hydrophilia of the agar blocks, it was concluded that it had done so by reducing the permeability of this colloidal material.

In conclusion, it is apparent that little is known about the mechanism of action of vitamin P. These substances are administered and the end results observed. There is a vast gap in knowledge concerning what transpires between these two points.

THE CLINICAL SIGNIFICANCE AND VITAMIN P THERAPY OF CAPILLARY-FRAGILITY STATES

Several types of vitamin P have been employed in diseases in which capillary weakness has been demonstrated or suspected. By controlling the capillary factor with vitamin P it has been possible at times to arrest a train of events that, if uninterrupted, would have imposed a serious burden upon the patient. The significance of the capillary weakness and results of vitamin P therapy are discussed below.

Allergic States

An increased capillary fragility has been found in allergy, this weakness and the vascular derangements, such as angioneurotic edema⁵⁰ and allergic purpura,⁵¹⁻⁵² have responded favorably to vitamin P therapy. No information is available on the nonvascular aspects of allergy in human beings. A report by Rapaport and Klein⁵³ on the value of vitamin P in correcting capillary fragility in allergic children makes no mention of the effects of vitamin P, if any, on the allergic diseases from which these children suffered.

Animal studies indicate that pretreatment with vitamin P fails to inhibit the acquisition of the hypersensitive state,⁵⁵ and most observers agree that it does not suppress the antigen-antibody

reaction.⁵⁵⁻⁵⁴ The claims that vitamin P prevents anaphylactic death in normal animals⁵⁵ have not been substantiated. However, it appears that vitamin P does stabilize certain peripheral substrates against the action of metabolites released during the antigen-antibody reaction. Thus, vitamin P could partially offset the action of histamine when the capillary wall was the substrate.⁵⁶ When smooth muscle of bowel, bronchus or vascular tree was the effector organ, no antihistamine power could be demonstrated.⁵⁵⁻⁵⁵⁻⁵⁶ Even with relatively tremendous doses of rutin, no antihistamine activity could be elicited in intact rabbits when the effector organ was the smooth muscle of the pulmonary-artery tree.⁵⁶ In summary, it is generally agreed that there is a capillary weakness in allergic states that may be corrected by vitamin P. The cause of the capillary dysfunction is unknown. Possibly, the weakness is due to excessive activity of trypsin, which is said to be capable of digesting interendothelial cement.⁵⁷

Natural Hemorrhagic Diathesis

Although coagulation disturbances are generally considered to be the prime cause of bleeding in conditions such as thrombopenic purpura, leukemia and aplastic anemia, Roskam,⁵⁸ in 1921, and subsequently others⁵⁹ have regarded the platelet factor as secondary in importance to a capillary defect. Even in hemophilia,⁶⁰ it has been suggested that a capillary disturbance may be of importance as well as the hypocoagulability of the blood. In animals, experimental thrombopenia fails to produce bleeding. Capillary damage must also be present.⁶¹ After splenectomy in thrombopenic purpura, it has been claimed that cessation of bleeding paralleled recovery from the capillary defect more closely than restoration of the platelet count.⁶¹ McFarlane⁶² has shed some light on the nature of the capillary factor. He has described structural changes in capillaries of adults suffering from vascular and thrombocytopenic purpura. In normal persons closure of capillaries was found to be an important factor in arresting capillary bleeding. In the above conditions, post-traumatic capillary closure failed to occur. It would be of interest to know if this capillary contractility returned after splenectomy, but no mention was made of this.

In vascular purpura¹ and hereditary hemorrhagic telangiectasia,⁶³ vitamin P has been able to arrest bleeding. In these conditions a simple mechanical weakness seems to operate, and may be reinforced by vitamin P. In thrombocytopenic purpura,¹⁻⁶⁴ in which a multiplicity of factors are involved, vitamin P has proved to be of no value. The compounds used so far do not stimulate capillary contractions. In view of McFarlane's findings of capillary atony, it would be interesting to try the catechins in this disease since they strongly stimu-

quercitrin and quercetin derivatives of rutin, produce a depressor response attributed to arteriolar dilatation. Intravenous administration of rutin itself has little or no effect on the blood pressure of cats³⁴ and dogs³⁵.

The catechins are unique in their ability to stimulate capillary vasomotion.³⁴

All types of vitamin P inhibit the oxidative destruction of epinephrine.³³ Some of them also partly simulate the action of that substance. For example, rutin and its aglycone, quercetin, both relax the guinea-pig colon.³³

TOXICITY

The only evidence of possible toxic manifestations of vitamin P is the depressor response that dogs exhibited after the intravenous injection of some of these compounds, and the depressor response that a patient with malignant hypertension experienced when 300 mg of hesperidin methyl chalcone was injected intravenously.³¹ The latter compound has been administered to human beings in oral doses up to 15 gm without any detectable adverse effects. Solutions of rutin have been injected in animals in amounts up to 500 mg per kilogram of body weight without any evident acute toxicity.³⁶ Rats fed diets containing naringin, hesperidin or rutin in amounts up to 1 per cent for as long as two hundred days did not show any signs of toxicity. On histologic examinations of the organs of the rats fed hesperidin and rutin, the tissues appeared normal.³⁷ Rutin in doses up to 500 mg daily has been administered to human beings orally, and no toxic signs could be ascribed to this therapy.³⁸

Evidence suggests that vitamin P, in addition to being free of toxic characteristics, reduces the toxicity of protoplasmic poisons such as heavy metals³⁹ and thiocyanates.¹⁹

MECHANISM OF ACTION

Capillary-Vasomotion Theory

The mechanism of the regulation of capillary resistance and permeability by vitamin P is, as yet, poorly understood. The first theory, proposed by Parrot and Lavollay,⁴⁰ was that vitamin P substances affected the capillaries indirectly by inhibiting the oxidative destruction of circulating epinephrine. The authors found that flavones inhibited the oxidation of epinephrine in vitro and that they prolonged the action of epinephrine on the colon and seminal vesicles of the guinea pig.³⁴ The claim that the flavones had no direct action on the guinea-pig viscera was subsequently disproved, but the epinephrine-sparing action of vitamin P has been substantiated.³³

Adrenochrome Theory

The epinephrine theory was modified⁴⁰ when it was found that a latent period of ten to thirty

minutes elapsed before a rise in capillary strength could be detected after the injection of this hormone into guinea pigs and human beings. This was in contrast to the usual promptness of the classic action of epinephrine, and it was postulated that the capillary changes were mediated by one of the early products of epinephrine metabolism, such as adrenochrome. This viewpoint was strengthened by the findings that various nonpressor adrenochromes⁴¹ increased capillary resistance in normal human beings and normal and scorbutic guinea pigs. Although the capillary-vasomotion theory was thus rejected, it was recently revived by others,⁴¹ who found that the catechins markedly stimulated capillary contractions. However, this theory still appears to be untenable since purified *d*-catechin, which stimulated capillary contractions, was, in the hands of others, shown to be devoid of vitamin P activity.

The adrenochrome theory was later expanded to include histamine as its chemical antagonist. This seemed plausible, particularly when antihistaminics were found to increase capillary resistance. Scorbutic guinea pigs demonstrated an increased sensitivity to histamine that could be restored to normal by vitamin P. However, in normal animals, vitamin P failed to neutralize the effects of histamine on the intact animal or the isolated colon. Thus, it was concluded that vitamin P did not directly antagonize histamine but that it reacted with the tissues so as to prevent histamine from increasing their permeability.⁴² The failure of vitamin P to demonstrate antihistamine activity in the normal animal does not correspond with the increase in capillary resistance observed in normal persons after the administration of vitamin P or adrenochrome. This casts considerable doubt on the histamine aspect of the theory, as does the observation that histamine is not a physiologic regulator of capillary permeability.⁴³ The increased susceptibility of vitamin P deficient animals to histamine is probably a reflection of a generalized nonspecific increase in tissue permeability that these animals acquire. In such animals, even an inert substance such as saline solution, when injected intradermally, diffuses more extensively than normally.⁴⁴ If a physiologic antagonist of vitamin P does exist, a more likely suggestion is hyaluronidase.⁴⁵

Epinephrine-Pituitary-Target-Gland Theory

Another mechanism has suggested itself on the basis of the epinephrine-sparing action of vitamin P. This theory suggests that the ultimate factors acting on the tissues are the hormones of the adrenal cortex and, possibly, the parathyroid glands. It is known that epinephrine causes a discharge of the anterior pituitary gland that, in turn, leads to an increased output from the various target glands.⁴⁶ The adrenocortical hormones have been shown to

increase the strength of capillaries,⁴⁷ and the parathyroid hormone to increase the resistance of the connective tissue.⁴⁸ Thus, vitamin P is visualized as regulating capillary resistance by an endocrine mechanism based on the ability of epinephrine to mobilize the pituitary gland and its target glands. It is not yet known whether adrenochromes can emulate this action of epinephrine on the endocrine system. Since adrenochromes are devoid of most of the properties that limit the administration of epinephrine, such information might be of considerable practical as well as academic interest.

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late capillary vasomotion. In a single case of hemophilia, Raunert⁶⁵ claimed that two intravenous injections of citrin given several hours apart were followed within twenty-four hours by cessation of bleeding, whereas the usual measures had been ineffective over a four-week period. However, as in all cases in which multiple therapy is given, the question of which agent produced the clinical response is problematic.

Radiation Disease

Over a period of years, it has become evident that hemorrhage following radiation may be due to at least three factors: thrombopenia,⁶⁶ capillary damage⁶⁷ and the presence of a heparinoid substance in the circulation.⁶⁸ The role of thrombopenia has been discounted because bleeding does not necessarily coincide with reduction in platelet counts.⁶⁸

Mathewson⁶⁸ was the first to use vitamin P for the control of radiation hemorrhage. Severe retinal hemorrhages developed in a patient receiving irradiation by spray technic for multiple myeloma. After vitamin P therapy the retinal bleeding stopped, as did hemorrhages from the nose and bladder, the latter antedating the x-ray therapy. Bleeding recurred when vitamin P was withdrawn and stopped again when the vitamin therapy was resumed. Mathewson stressed the importance of the capillary factor in x-ray therapy and suggested the prophylactic use of vitamin P to reduce the danger of hemorrhage from this type of treatment. Experimental confirmation of this suggestion has been brought forth by Reckers and Field.⁶⁹ Fifty dogs were subjected to a single exposure of 350 r. Twenty-five served as controls, and of these, 16 (64 per cent) died in thirteen to thirty days. All 16, as well as 3 of the survivors, showed widespread hemorrhagic phenomena. The other 25 dogs were treated with rutin orally, 50 mg three times a day beginning one week before radiation. Of this treated group, only 3 (12 per cent) died. All the survivors of the rutinized group, as well as 1 of the 3 that died, were relatively free of petechiae and ecchymoses during the post-radiation period, and when autopsied at forty to sixty days. In addition, several rutinized dogs survived a severe leukopenia lasting from ten to fourteen days. The authors stated that in their previous experience, spontaneous recovery from severe radiation leukopenia of this duration was extremely rare. In mice⁷⁰ rutin failed to prevent death from radiation, but it must be noted that, in this species,⁷¹ hemorrhages are frequently difficult to find and are not an important cause of death. It therefore seems that the protective action of rutin, as in other instances, is largely confined to the vascular tree.

After the explosion of atomic bombs, three types of energy are liberated: blast, heat radiation and

ionizing radiation.⁷² The last is said to induce pathologic changes identical to those resulting from overdosage of irradiation. At Hiroshima and Nagasaki,⁷³ the exposed persons who survived the blast and heat effects developed an illness similar to that which Shouse and his co-workers⁷⁴ and Reckers et al.⁶⁹ had produced in dogs with overdosage of x-rays. All the formed blood elements were reduced, mostly owing to destruction of bone marrow. Terminally, petechiae appeared in the skin, and blood oozed from the body orifices. At autopsy, hemorrhages were found in the tissues and viscera, including the brain, meninges, kidneys and gastrointestinal tract.⁷⁵ Of the 125,000 deaths resulting from the atomic explosions it has been estimated that from 8 to 20 per cent were due exclusively to radiation effects.⁷² In view of the importance of hemorrhages as a cause of death in these cases, the ability of rutin to inhibit radiation-induced bleeding is of obvious significance. In addition, it has been shown that rutin accelerates the recovery of tissues burned by overdosage of x-ray.⁷⁶ Several investigators⁷⁶ found that the degenerated bone marrow of many of the survivors retained a regenerative capacity, and they stated that if advantage had been taken of this feature, the death rate from ionizing radiation would have been much lower. These findings suggest a possible prophylactic value of vitamin P in persons subjected to ionizing radiation for therapeutic or other purposes. The findings are of such potential significance that ample confirmation of these observations is eagerly awaited.

Dicumarol Therapy

The occurrence of hemorrhage after administration of Dicumarol does not necessarily parallel the prolongation of the prothrombin time. Bleeding has occurred with only moderate depression of prothrombin activity, and conversely, when the prothrombin has been excessively prolonged, expected hemorrhages have frequently failed to materialize. For this reason, factors other than hypocoagulability of the blood have been sought that might have a bearing on bleeding. Wright and Prandoni⁷⁷ have shown that, even when Dicumarol produces hemorrhage, there is no increase in capillary fragility. However, in dogs given Dicumarol, Bingham, Meyer and Pohle⁷⁸ found marked dilatation of capillaries, small arteries and veins. This suggested a vascular component for the institution of bleeding—a viewpoint that has been stressed by Quick.⁷⁹ McLean and Brambel⁸⁰ gave rutin to patients receiving Dicumarol, but since none of the controls bled, the effects of rutin could not be judged. Clark⁸¹ administered sufficient Dicumarol to rats to induce bleeding and found that rutin given orally failed to prevent the hemorrhages. Since in these experiments the rats may have succumbed before

the latent period of rutin activity expired, Levitan and Schwager⁵² carried out similar experiments in rabbits, using esculin, which is a potent, quick-acting type of vitamin P. Like rutin, esculin failed to prevent the hemorrhages. Neither rutin nor esculin produces capillary contractions. In view of the pathological evidence of vascular engorgement in Dicumarol poisoning, it would be of interest to test the catechins in this condition since they are said to stimulate vasomotor activity.

Degenerative Vascular Disease

As arteries degenerate, newly formed capillaries appear about the atheromatous plaques in the intima.⁵³ These intimal capillaries⁵⁴ are distinct from the vasa vasorum, which lie in the outer half of the artery wall, and appear only after arteriosclerosis has progressed to a moderate degree. Their role in the pathogenesis of coronary and cerebral thrombosis has been established by Paterson⁵⁴ and confirmed by others.⁵⁵ When the capillaries rupture, an intimal hemorrhage that leads to the development of a thrombus in the adjacent lumen is formed. The suggestion that a similar mechanism operates in cerebral hemorrhage⁵⁶ apparently stimulated Griffith and Lindauer^{19, 33} to study the role of capillary fragility in cerebral and retinal hemorrhages complicating hypertension. They confirmed Levrat's⁵⁷ finding that the incidence of such complications was considerably greater when an increased capillary fragility was present. Numerous studies since 1872^{58, 59} have shown that capillaries deteriorate in arteriosclerosis, and hence the finding of an increased fragility in such circumstances reflects a diffuse vascular degeneration. The correlation between positive fragility tests and a high incidence of vascular accidents thus becomes apparent. Griffith and Lindauer³³ claimed that they could correct the capillary weakness in 75 per cent of such cases by the use of rutin, and concomitantly, the incidence of cerebral and retinal hemorrhages was reduced. Unfortunately their control group consisted of the 25 per cent whose capillary defect failed to respond to rutin, because of either insufficient or intermittent dosage. This choice of a control group complicates an evaluation of their findings. Other investigators,⁶⁰ in smaller series of cases and over relatively short periods of observation, have obtained varied results. Final conclusions regarding the effects of rutin on the vascular complications of hypertension cannot be made from the data available at the present time.

Diabetes Mellitus

Numerous workers have found a high incidence of increased capillary fragility in this disease, par-

ticularly when retinopathy is present.^{61, 62} This is partly due to the premature development of arteriosclerosis. The retinopathy, however, depends on factors in addition to arteriosclerosis. Changes in plasma proteins that were more pronounced in cases complicated by retinopathy have been found.⁶³ An endocapillary layer of protein has been described by Danielli⁶⁴ as an integral part of the capillary wall that regulates pore diameter. A disturbance of this layer secondary to the changes in plasma proteins might contribute to the retinopathy by increasing the size of the pores so as to allow the escape of blood constituents that go to form the hyaline plaques.

Several types of vitamin P have been used to control the retinopathy. The results have not been dramatic.^{1, 91, 92} Objective improvement has not been attained, but it appears that the degenerative process has been arrested in patients whose capillary fragility returned to normal. According to Rodriguez and Root,⁹¹ this may not be achieved until many months of intensive therapy have elapsed. It appears, then, that little can be expected from vitamin P therapy in diabetic retinopathy unless large doses are administered indefinitely.

Frostbite

The capillary damage that occurs in this condition prompted Fuhrman and Crismon⁹⁵ to study the effects of rutin in frostbite. Large doses of rutin administered to rabbits prior to or shortly after the extremities were subjected to low temperatures markedly reduced the extent of subsequent gangrene. However, these effects of rutin were not reproducible when the ears were the test object.

Albuminuric Diseases

Dunn⁹⁶ states that Cohnheim originated the idea that damage to peripheral capillaries was important in the development of renal edema. Some support for this concept is afforded by the findings of Göthlin⁹⁷ that capillary resistance is decreased in albuminuric conditions. Although the cause of this change is unknown, two possibilities are present. Glomerulonephritis and its variant, lipoid nephrosis, are believed by many to develop on the basis of an acquired sensitivity to streptococcal toxin, and as was previously shown, capillary fragility is increased in allergic conditions. Thus, an increased capillary fragility and permeability of an allergic nature may explain the early formation of edema, before plasma proteins are significantly reduced. The loss of albumin through visibly damaged glomeruli might also contribute to the capillary damage by disrupting the endocapillary layer.

Several authors have used vitamin P in various nephritides. Again the results are contradictory.^{1 98, 99} Further work is required, particularly with injectable preparations.

Dermatologic Conditions

Goldfarb¹⁰⁰ has used citrin therapy in psoriasis, based on Wertheim's description of morphologic capillary alterations in this disease. Of 45 patients treated 30 were said to have improved on the basis of diminution in the infiltration of the lesions and a decrease in scaling. In only 2 patients did the lesions completely disappear. In a variety of dermatologic conditions, crude hesperidin and hesperidin methyl chalcone administered for ten days to three weeks have proved to be of little value.¹⁰¹

Miscellaneous

Several reports have appeared on the use of rutin in bleeding of obscure origin. Schwager⁹² administered rutin, 20 mg three times a day, to a five-year-old girl with a history of epistaxis recurring three to six times weekly for several months. The only abnormal finding was an increased capillary fragility. After a month of rutin therapy, the capillary strength became normal, and the bleeding stopped. During an eighteen-month follow-up period, only one nose-bleed occurred, in the course of an upper-respiratory-tract infection. Shanno⁹⁴ reported 2 cases of hemoptysis, and Zfass¹⁰² 1 case of hematemesis of obscure etiology that responded favorably to rutin. In both reports the capillaries were excessively fragile prior to rutin therapy.

FIELDS FOR FUTURE STUDY

In spite of the widespread application of vitamin P, there remain several commonly occurring diseases in which it has yet to be applied. These include schizophrenia, cryptogenic epilepsy, migraine and Ménière's syndrome, in all of which capillary disorders appear to be of importance.

Capillary microscopy has revealed bizarre morphologic abnormalities in schizophrenia, and the weakness of these vessels is borne out by their directly observed tendency to rupture spontaneously.¹⁰³ An increased capillary permeability has also been detected by the technic of blister formation.¹⁰⁴ The possibility that recurring episodes of petechial hemorrhages in the brain substance contribute to the mental deterioration and the possible interruption of this process by vitamin P makes interesting speculation.

In cryptogenic¹⁰⁵ and deteriorated types¹⁰⁶ of epilepsy and in migraine,¹⁰⁶ which is genetically related to epilepsy, structural abnormalities of capillaries have been described. During attacks of migraine an actual increase in capillary permeability has been observed,¹⁰⁷ as indicated by blurring of capillary outlines. Similar changes have occurred premenstrually,¹⁰⁷ at which time migraine

attacks are prone to occur. Migraine is frequently precipitated by emotional conflict, which is also said to increase capillary fragility. These considerations, as well as the claim that vitamin P prevents the increased fragility that occurs in emotional stress,¹⁷ suggest a trial of vitamin P therapy in these diseases.

In Ménière's disease,¹⁰⁸ edema of the labyrinth has been implicated, and in view of the probable capillary basis for the edema, this syndrome merits a trial of vitamin P therapy.

The more recently discovered types of vitamin P, such as the catechins and esculin, also deserve further clinical application particularly in view of their potency, moderate solubility in water and rapid absorption from the gastrointestinal tract. Both may be given parenterally in aqueous solution. Rutin, the current popular type of vitamin P, is practically insoluble in water and must be dissolved in alkali alcohol, pyridine or propylene glycol for parenteral use. Clinically, rutin has been given only by mouth. Its absorption and excretion have not as yet been studied, and except for clinical response, there is no proof that it is absorbed from the gastrointestinal tract. Although it is possible that the long latent period observed in the clinical use of rutin is due to the nature of the pathologic condition being treated, it may also be referable to poor absorption from the intestines. Further work is required to clarify this point. The capillary vasomotor stimulation that the catechins alone exhibit³⁴ suggests their application in diseases such as thrombocytopenic purpura in which capillary atony is said to be an important factor in the genesis of bleeding.⁶²

Although almost all the investigations carried out to date are concerned with capillaries, recent evidence suggests that vitamin P is concerned with the stability of the system of ground substance of which that present in capillaries is only a small part. The ability of spreading factors to increase the permeability of connective-tissue ground substance has been reduced by vitamin P^{44 109} and enhanced by anti-vitamin-P factor.⁴⁴ The significance of this observation lies in the number of diseases to which ground substance falls prey. Abundant data have been accumulated¹¹⁰ indicating that the spread of infections and malignant growths is partly determined by the degree of permeability of ground substance. The stabilizing effect of vitamin P^{44 109} is thus of obvious significance. Ground substance is probably present in the erythrocyte membrane, and its stabilization by vitamin P is suggested by the increased resistance that erythrocytes treated with vitamin P demonstrate when exposed to hypotonic saline solution.²⁴ This observation raises the problem of a possible relation between vitamin P and hemolytic and aging processes of the red blood cell. Ground substance is present in the artery wall,^{89 111} and in experimental arteriosclerosis it has been

clearly shown that alteration or damage of this ground substance takes place before lipoids are deposited in it.¹¹² That vitamin P stabilizes arterial ground substance is suggested by the claims that rutin reduces the incidence of cerebral hemorrhage in hypertension.²⁵ Although this study was undertaken on the assumption that intramural capillary hemorrhage might determine the occurrence of cerebral hemorrhage, such a mechanism has never been clearly demonstrated in this type of vascular accident. It is generally believed that cerebral hemorrhage is due to an elevated arterial pressure rupturing the entire thickness of a weakened vessel wall. Since little or no change in blood pressure has been observed in such cases treated with rutin, the beneficial effects appear to be due to local stabilization of the vessel wall. With these considerations in mind, I attempted to study the effects of rutin on the prevention of experimental arteriosclerosis in rabbits. Uncontrollable factors twice reduced the number of surviving animals so as to preclude definite conclusions, but some protection seemed to be afforded by rutin. There is ground substance present in intervertebral disks, probably hyaluronic acid.¹¹³ The interesting hypothesis has been advanced that disk degeneration is due to disease of the ground substance of the disk and, as such, reflects a widespread ground-substance degeneration, possibly owing to repeated infections caused by hyaluronidase-producing organisms.¹¹⁴ If this is true, the ability of vitamin P to stabilize ground substance against the action of hyaluronidase^{115, 116} is again of obvious importance.

Increasing attention is now being directed to the role of mucus in the prevention of peptic ulcer and chronic ulcerative colitis. Meyer and his co-workers^{115, 116} have shown that the enzyme lysozyme, which is capable of digesting mucus, is present in high concentration in the gastric juice of patients with peptic ulcer and in the stools of patients with chronic ulcerative colitis. They have suggested that dissolution of the mucin coating by lysozyme activity exposes the bare gastrointestinal mucosa to the eroding action of hydrochloric acid and indigenous bacteria. The protective action that gastric mucin affords the gastric mucous membrane has been clearly demonstrated. The mucosin sulfuric acid of gastric mucin is closely related to the hyaluronic acid and chondroitin sulfuric acid of connective-tissue ground substance.¹¹³ The ability of vitamin P to stabilize the ground substance raises the question whether a similar effect might be exerted on gastrointestinal mucin. In this connection, it may be more than coincidental that cabbage juice, which has been claimed to accelerate the healing of peptic ulcer,¹¹⁷ is a rich natural source of vitamin P. Other conditions that suggest themselves for vitamin P studies are the collagen diseases and amyloidosis.

In conclusion, vitamin P studies have been made in numerous diseases in which capillary defects appear to play a role. The purpose of this paper is to review these findings and to direct attention first to other diseases in which capillary factors appear to be of importance and secondly to diseases of ground substance that might provide interesting material for future vitamin P investigation.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



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CASE 35461

PRESENTATION OF CASE

A sixty-three-year-old laborer entered the hospital complaining of epigastric pain.

He had been well until eight years before admission, when he developed burning epigastric pain. There was no relation to meals. His physician prescribed a "white stuff," which relieved the pain but caused constipation. A gastrointestinal series at that time was negative. The pain disappeared after a few weeks and did not return until two years later, when there was a similar attack. The third episode occurred six months before admission. The pain usually came on when he was hungry, beginning in the midepigastrium and radiating toward both flanks. It occurred daily, one to four hours after meals, and was relieved by food, milk and the white medicine. His worst attack began three weeks before admission, the pain was more severe than ever, but was still relieved by food and sometimes by the passage of flatus. There had been no nausea, vomiting, change in bowel habit, melena or grossly bloody stools. There had been little weight loss, the weight on admission being 165 pounds, one year previously, it had been 170 pounds.

Physical examination revealed a well developed and well nourished, muscular man in no discomfort. The anteroposterior diameter of the chest was increased. The lung fields were hyperresonant. The heart was normal. There was slight tenderness without spasm in the midepigastrium. The costo-

vertebral angles were slightly tender. No masses other than what appeared to be feces in the colon were palpable.

The temperature was 99°F, the pulse 74 and the respirations 20. The blood pressure was 138 systolic, 78 diastolic.

Laboratory studies revealed a red-cell count of 5,000,000, with 14 gm of hemoglobin, and a white-cell count of 9600, with a normal differential count. Urinalysis was normal. The total protein was 7.4 gm, the nonprotein nitrogen 29 mg, and the fasting blood sugar 81 mg per 100 cc. A stool was guaiac negative.

A gastrointestinal series revealed a deeply penetrating ulcer in the midportion of the posterior wall approaching the greater curvature. It measured 2 cm in width and 3 cm in depth. About the ulcer there appeared to be a good deal of soft-tissue swelling. Barium passed the pylorus without hesitancy, filling the duodenal bulb to its normal contour.

A gastroscope was introduced, and normal, rather active peristaltic waves were seen passing over a normal-appearing antrum. Just proximal to the angulus of the greater curvature, an ulceration, sharply punched out and measuring 1.5 cm in diameter, was noted. The margin was sharp and surrounded for a distance of 2 cm by a flat, plateau-like area in which no rugae were present. The lesser curvature, from a distance of about 2 cm above the ulcer down to the pylorus, was rigid and shortened. Not enough barium passed into the duodenum to fill out the duodenal bulb to normal contour. No barium left the stomach by way of any anastomosis.

A fasting gastric aspiration failed to produce free acid, but free acid was present after histamine. The patient was kept virtually pain free by hourly feedings. The temperature and white-cell count fell to normal. The morning gastric residual fluid was reduced from 300 to 75 cc during the first week. On the seventeenth day, gastroscopy revealed a constantly deformed and rigid-appearing angulus. Its outline was irregular and slightly nodular. No peristalsis was visible. The ulceration seen at fluoroscopy was out of the range of the gastroscope.

Three days later, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CLAUDE E. WELCH* We may as well start by seeing the x-ray films to get all the data

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CLINICAL DIAGNOSIS

Gastric ulcer

DR WELCH'S DIAGNOSIS

Benign gastric ulcer

ANATOMICAL DIAGNOSIS

Benign gastric ulcer, greater curvature

PATHOLOGICAL DISCUSSION

DR CASTLEMAN On the posterior surface along the greater curvature, 9 cm from the proximal resection edge, was a perforated ulcer, partly walled off by the adjacent mesocolon, omentum and pancreas. When the stomach was opened the lesion was sharply punched out, and its grossly benign appearance was confirmed microscopically.

CASE 35462

PRESENTATION OF CASE

First admission A fifty-seven-year-old housewife was admitted to the hospital because of vomiting and a spontaneous black eye.

She was apparently well until four weeks before entry, when she developed a severe lumbosacral pain radiating at times to the left leg, not relieved by strapping and continuing intermittently until she entered the hospital. She also noted blood in the stool as well as some blood on the nightgown. Three weeks prior to admission she entered a community hospital for vaginal bleeding, the first since her menopause ten years previously. No diagnosis was made, and she was discharged after three days. One week before entry a rash appeared on the medial aspects of both legs and thighs. Four days before admission she developed mild vomiting and anorexia. There was no blood or bile in the vomitus.

The past history revealed an episode of pain in the right upper quadrant, with vomiting and jaundice, two years prior to admission. A cholecystostomy was performed, with the removal of several gallstones. The patient had been known to have mild diabetes for an indefinite period.

Physical examination revealed a well developed, moderately obese woman who was not acutely ill. There was a fading papular rash over both posterior thighs and lateral aspects of the knees. There were right periorbital and scleral areas of ecchymosis. The lungs were clear. The heart was slightly enlarged to the left, and a Grade II, harsh systolic murmur was audible at the apex. Abdominal examination showed slight diffuse tenderness referred to the upper quadrant and some tenderness in both costovertebral angles. Pelvic and rectal examinations were negative. Examination of the fundi showed a few flame-shaped hemor-

rhages, with arteriolar narrowing and blurring of the disk margins, without papilledema. There was a questionable slight left facial weakness. Tendon reflexes were hypoactive throughout, but there was no asymmetry. Ankle jerks were absent bilaterally. Both plantar responses were down or absent. There was no weakness of the extremities. Sensation was intact, co-ordination was accurate.

The blood pressure was 140 systolic, 95 diastolic. The pulse was 85, and the respirations 20.

Urinalysis revealed a specific gravity of 1.020, a ++ test for albumin and intermittent green in the sugar reactions. A catheterized specimen showed 30 white cells per high-power field but no red cells or casts in the sediment. There was no bile or Bence-Jones protein. Examination of the blood revealed an initial hemoglobin of 11 gm, slowly falling to 8 gm. The white-cell count was within normal range, the platelets were adequate. Repeated determinations of the clotting time, prothrombin time, capillary fragility, bleeding time and platelet counts were within normal limits, as were the serum nonprotein nitrogen, the carbon dioxide combining power, the total protein, the calcium, the phosphorus, the amylase, the cholesterol and the cholesterol esters. The blood sugar ranged between 200 and 250 mg per 100 cc. The bromsulfalein test showed 36 per cent retention of the dye in forty-five minutes. The van den Bergh reaction rose from normal to 1.6 mg per 100 cc. The urine urobilinogen was 1.2 Ehrlich units in two hours. The thymol-turbidity and the cephalin-flocculation tests were negative. A blood culture was negative. An electrocardiogram revealed changes consistent with coronary-artery disease. An electroencephalogram was within normal limits. X-ray films of the chest were unremarkable except for some strand-like increase in density. Films of the spine, ribs, pelvis, hips and shoulders showed peculiar scattered areas of bone density. The second lumbar vertebra was denser than normal. Skull films were normal. A gastrointestinal series revealed no abnormalities. An intravenous pyelogram was normal except for a double pelvis in the right kidney. A bone-marrow aspiration showed marked stimulation of red-cell production. A vaginal smear was negative for tumor cells. A lumbar puncture revealed an initial spinal-fluid pressure equivalent to 400 mm of water, falling after fifteen minutes, relaxation to 300 mm. Three cubic centimeters of clear spinal fluid was removed, the total protein was 104 mg per 100 cc, no cells were present.

During the two-week period in the hospital the vomiting cleared and the ecchymoses of the skin and the right orbit faded somewhat. No new symptoms appeared. The diabetes was mild and was controlled without insulin. It was decided to observe the patient rather than to perform a craniotomy because of the symptoms of increased intra-

DR RICHARD SCHATZKI In addition to what is reported in the record I think I see something else that might be of significance. It seems to me that in these three films the lesser curvature is stiff over an area 5 cm in length. The crater may be seen in profile in this film. In this next film the crater cannot be seen because there is too much barium. This stiffness, which I assume to be present, is the ulcer. There is marked swelling around the ulcer.

DR ALFRED KRANES Are you able to tell that the wall is stiff without fluoroscopying the patient?

DR SCHATZKI I certainly prefer fluoroscopy. On the other hand several films may allow some judgment. The normal stomach changes constantly in shape, and an area that does not change is usually rigid. We have not many films here, and I would like to have my hands on the patient's stomach.

DR WELCH I do not know what disease this patient had, but, as an academic exercise, we shall recount the methods of differentiating benign and malignant ulcer. In the first place, patients in the older age group who have a long story of gastric distress are more likely to have benign than malignant lesions. The patient with a short history is rather likely to have cancer. On this basis, we are slightly inclined toward ulcer in this case. The position of the ulcer is of importance. Almost all ulcers on the greater curvature are malignant. Those on the anterior or posterior walls carry about a 20 per cent chance of malignancy according to our figures in this hospital. Since this ulcer was on the posterior wall close to the greater curvature, the diagnosis is indeterminate from that criterion. The determination of free hydrochloric acid is not of great importance. If it is absent, one is inclined toward a diagnosis of a malignant lesion, but if free acid is present, cancer cannot be excluded.

Another method of differentiation is by the rate of healing. No evidence is offered in this case since the patient was observed in the hospital for only eight days. Another method is afforded by the type of pain, but, in this patient, who had a deeply penetrating lesion of the pancreas with tenderness in the epigastrium, pain is sure to have been present regardless of the diagnosis of ulcer or cancer.

A final bit of evidence is offered by the cytologic smear of the gastric contents. If the specimen obtained is in good condition and cancer cells are not seen, the differential diagnosis is still dubious because about a third of the carcinomas of the stomach do not shed cells. However, if cancer cells are reported from our laboratory, the chances of error are almost zero.

Whether or not such an examination was made is not mentioned in the protocol.

There is some additional evidence that this patient had ulcer rather than cancer. He had no weight loss in spite of the fact that the lesion was large. Also, examinations for occult blood in the

stool were negative, and carcinoma is more likely to demonstrate this type of blood loss than is benign ulcer. The gastroscopic examination introduces a rather disturbing feature in that no peristalsis was observed around the margin. This is uncommon for ulcer and more typical of cancer, but in this particular patient, we have an element of pancreatitis superimposed because this lesion had perforated into the pancreas.

Considering all these features, the evidence is in favor of benign ulcer in this patient. The evidence is also strongly in favor of operation. An operation designed for cancer rather than an operation for benign lesion should be carried out.

DR WALTER BAUER I am trying to get Dr Kranes to bet on the possibility that this was not benign. I want to bet that it is benign.

DR SCHATZKI I do not like to bet in a case like this because I think the evidence is not conclusive. If I were to take a chance, I would say cancer.

DR MILFORD SCHULZ It is not a deeply penetrating ulcer. Considering that ulcer occurs following necrosis in a spindle-cell tumor, would Dr Schatzki like to say something about that and why he does not think it is one of that type?

DR BENJAMIN CASTLEMAN You mean an intramural extramucosal tumor?

DR SCHULZ Yes.

DR SCHATZKI From the evidence I would rather say no, but probably that is just what it is going to turn out to be. May I say one word about a statement Dr Welch made that an ulcer on the greater curvature is almost always malignant. I think that statement is based on surgical statistics, and roentgenologic statistics vary a bit because it depends on what one calls an ulcer of the greater curvature in one's statistics. In cases with any kind of ulceration of the greater curvature, there is an overwhelming number of cancers. If those that are grossly malignant are excluded and only the grossly benign lesions considered, the percentage of benign ulcers will go way up. I remember at least 3 or 4 ulcers of the greater curvature in this hospital that turned out to be benign. Statistics will vary among hospitals. In an active hospital the number of benign cases will go up because many more benign lesions will be operated on, it also depends considerably on the x-ray interpretation.

DR CHARLES MIXTER, JR A cytologic smear was made, but it was unsatisfactory. At the time of operation the lesion was grossly benign. It was close to the greater curvature and appeared to invade the pancreas and transverse mesocolon. In view of the position of the lesion and because of apparent invasiveness we treated it as carcinoma and therefore elected to take out the tail of the pancreas and also a part of the transverse colon.

vertebra, and I believe there is an area of destruction in the margin of the second lumbar vertebra with slight compression of the body of this vertebra. Small radiolucent areas are seen in the lower ribs. Examination of the chest, made on the first admission, shows a strand-like increase of density throughout both lung fields and small nodules in the peripheral lung fields. A film made on the second admission shows only a slight increase in the strand-like and nodular densities in both lung fields.

The films of the skull show one or two small radiolucent areas over the vertex having the appearance of venous lakes. The density extending across the parietal bones is due to a braid of hair. The sella turcica is normal in size and smooth in contour. There is no evidence of lesions in the skull. The calcified pineal body is in the midline.

DR BALBONI: Is there anything abnormal about the duodenum? There is no widening?

DR McCORT: There is no widening and no evidence of intrinsic involvement of the duodenal wall. The liver, as I mentioned previously, seems somewhat larger than normal.

DR BALBONI: Are the kidneys normal?

DR McCORT: Yes, the double kidney on the right is of no pathological significance.

DR BALBONI: It is rare but not impossible for metastases from a single tumor to be both osteoblastic and osteolytic. Is that the situation here?

DR McCORT: The changes in the bone are both osteoblastic and osteolytic.

DR BALBONI: With the help of the x-ray studies, the picture seems to be clearing a little bit. She had an x-ray picture of metastatic cancer, widespread throughout the skeleton, of both osteoblastic and osteolytic lesions and also lesions in the lung. The liver, which was not enlarged clinically, was slightly enlarged by x-ray study. There was abnormal function of the liver as manifested by the bromsulfalein retention. This was the only liver-function test that was abnormal, and it is consistent with involvement of the liver by tumor. I assume that part of the liver was destroyed by metastases but that the remaining liver cells were functioning normally and capable of performing all functions of the liver except excretion, which was somewhat reduced as evidenced by the bromsulfalein test and the van den Bergh reaction, which rose to 16 mg per 100 cc.

The common tumors that metastasize to bone are tumors of the breast, the prostate, the kidney and the bronchus. The only one I am sure was not involved here was the prostate, but there is little to suggest any of the others. The question of multiple myeloma in the bone, spreading widely through the pelvis, ribs and spine, has to be considered when one is confronted with lesions of this multiplicity, but such lesions are almost invariably osteolytic. Furthermore, at this stage of the game in multiple myeloma one would expect an elevated

serum protein, and sometimes an elevated serum calcium. The absence of Bence-Jones protein in the urine is not against the diagnosis because it only occurs in about 50 per cent of cases of multiple myeloma.

Osteoblastic lesions are usually very slowly growing lesions such as may be seen in tumors of the pancreas. It is difficult to locate the primary site of the cancer. We know that she had previous gall-bladder disease, and she could have had a malignant lesion that developed in the gall bladder. Usually, in that situation, a mass is palpable in the region of the gall bladder. This woman apparently had none. I cannot locate the source of the tumor but I think she died of metastatic tumor involving the brain, the spine, the pelvis, the lungs and the liver. It would be unusual to have this a granulosa-cell tumor of the ovary that became malignant and spread, but in view of the fact that she had vaginal bleeding and an estrogen effect in the vaginal smear and in view of the fact that she had not taken any estrogen orally that diagnosis has to be considered. I would also seriously consider the gall bladder and pancreas as the primary site for the cancer.

A PHYSICIAN: Is the elevated blood sugar significant?

DR BALBONI: She was known to have diabetes for a good many years, and I would think that the elevated sugar was consistent with her diabetes, which was aggravated by the surgical procedures she was subjected to.

DR GREENE FITZHUGH: The diagnosis on the Medical Service was metastatic cancer. Our opinion was that we should biopsy that mass in the pelvis before having a neurosurgeon see her because of the brain lesions, but she got worse so rapidly that we transferred her to the neurosurgeons in the hope that they might be able to prolong her life.

CLINICAL DIAGNOSES

Disseminated neoplastic disease, unidentified
Metastatic carcinoma of brain and lung
Diabetes mellitus

DR BALBONI'S DIAGNOSES

Metastatic cancer involving brain, spine, pelvis, lungs and liver
? Granulosa-cell cancer of ovary, ? cancer of gall bladder, ? cancer of pancreas

ANATOMICAL DIAGNOSES

Carcinoma of gall bladder, with extension to extrahepatic bile ducts and peripancreatic nodes, and metastases to lungs and bones
Cholelithiasis, with obstruction of ampulla of Vater
Arteriosclerosis, generalized

cranial pressure On the fifteenth hospital day she was sent home to be followed in the Out Patient Department

Final admission (six days later) After a very short stay at home the patient was readmitted because of increasing back pain and recurrence of the vomiting

The neurologic examination remained unchanged The fundi, however, revealed advanced papilledema and recent hemorrhages Sensory changes were equivocal Her mental state, which had been extremely poor, was unchanged

On the fifth hospital day bilateral anterior temporal burr holes were made to rule out subdural hematoma The right side revealed a thickened dura but no subdural fluid Bleeding during the procedure was very profuse and difficult to control On the following day she had a left hemiparesis of the face and upper extremity Re-exploration revealed a recent operative blood clot in the right frontal burr hole After enlargement of the incision no subdural accumulation of fluid was discovered Dural and bone bleeding was controlled, but during the evening after operation oozing was noted over the bandage Gradually, the patient became more comatose, and the blood sugar ranged from 350 to 450 mg per 100 cc On the eighth hospital day a right subtemporal decompression was performed because of jerking movements of the left arm and hand, suggesting possible subdural hematoma, but none was found A repeated x-ray film of the chest showed an increased number of nodular densities

During the following days the patient progressively deteriorated She became very pale, the blood pressure dropped, and she died on the twentieth hospital day

DIFFERENTIAL DIAGNOSIS

DR VICTOR G BALBONI* We are dealing with a woman in late middle age who a month before entry developed severe back pain At about the same time, she had vaginal bleeding and then vomiting, for which she was admitted to the hospital She was found to have ecchymoses about the eye, and a rash, which may have been a purpuric rash although the record is not clear on that The vaginal bleeding, the rash, the ecchymoses about the eye and the fact that later on she developed signs of an intracranial lesion raise the question of whether she had some form of bleeding tendency or purpura However, the bleeding time, the clotting time, the prothrombin time and the tourniquet test were all within normal limits Therefore it seems untenable to entertain seriously a diagnosis of purpura to account for the clinical course of this patient The leg rash, I cannot explain The ecchymoses about the eye, I think, may be explained on the basis of rupture of normal or slightly arterio-

sclerotic vessels while she was vomiting for four days She had mild diabetes and was entitled to some vascular disease

Vaginal bleeding is a much more important symptom, and in any woman of this age means cancer of the genital tract until proved otherwise Pelvic and rectal examinations were negative We are told that she had a previous hospital entry for three days, and I wonder if dilatation and curettage were done at that time It would seem like a logical thing to do on a woman who was bleeding, but we have no information about that A functioning ovarian tumor, a granulosa-cell tumor, may cause resumption of vaginal bleeding any time after the menopause, but granulosa-cell tumors are rarely malignant Later on there is evidence that she had a malignant tumor with widespread metastases Granulosa-cell tumors can become malignant and metastasize, but usually they do not The vaginal smear showed no evidence of cancer cells That is fairly good evidence against a malignant lesion of the uterus It does not completely rule it out, however Sometimes in reports of vaginal smears, the presence or absence of an estrogen effect in the cells is noted I wonder if it was in this case

DR JOHN W LITTLEFIELD Yes, there was a marked estrogen effect in the smears

DR BALBONI That raises another question A not uncommon cause for vaginal bleeding in a woman of this age is oral or parenteral estrogenic medication

A PHYSICIAN There was no history that she had been taking estrogenic medication

DR BALBONI The fact that she showed an estrogen effect in the vaginal smear indicates that she had been taking estrogenic substances or that she had a functioning tumor of the ovary—a tumor making estrogen

Later in the clinical course signs of increasing intracranial pressure developed, and the questionable right facial paralysis she showed on entry became very definite In other words, she apparently had a lesion within the skull, and it probably was getting larger The x-ray films show lesions in many of the bones and in the lung and from the description I gather that they were osteoblastic metastases We might well review the films now

DR JAMES J MCCORT On the intravenous pyelogram a double kidney is seen on the right side The liver edge is lower than normal A study of the gastrointestinal tract discloses a normal esophagus, stomach and duodenum No widening of the duodenal loop is seen The colon was examined on two occasions and shows no intrinsic abnormality On the films made of the colon it is noted that there are small densities present throughout the bones of the lower ribs, the lumbar spine and the pelvis These densities are irregular and of varying size, extending up to 2 cm in diameter There is also increased density of the second lumbar

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THANKSGIVING

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place to sleep. They can be thankful for freedom of speech under most circumstances, for freedom of action if it does not offend the majority or more powerful interests, and for freedom in selecting the type of medical care that is most suited to their needs.

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BANNER WITH A STRANGE DEVICE

AMONG the activities associated with the United Nations the World Health Organization stands out as one of the most promising. Its program is reasonable and reminiscent of the good old days before 1914 when the civilized nations united in all sorts of mutually beneficial activities, such as uniform postal rates, copyright laws, weather reports, public-health regulations, the gold standard and hydrographic surveys, and global war had not been heard of since Waterloo except in the nightmares of H. G. Wells. If all nations could really agree on the importance of achieving world health, most other problems would be solved for nothing is unhealthier than war and its sequelae.

Medical knowledge has kept pace with the technical advances that have marked a century of progress. This is what the chief of the American delegation to the second World Health Assembly, held in Rome from June 13 to July 2, may have had in mind when he declared in his report: "Unless we move forward to improve the health of mankind it is impossible for mankind to move forward." The statement suggests a pleasing slogan: *Gesundheit et excelsior!* What might the nations accomplish if united under a banner with such a device?

Of course there is the risk that when mortal disease is abolished man will propagate so unrestrainedly that the world will be overpopulated in a few generations and that people will then die off, in

Operative scars cholecystostomy, old, frontal burr holes, recent, subtemporal decompression, recent

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Autopsy on this patient disclosed a small, extremely firm, shrunken gall bladder, with thickened walls and some palpable excrescences of the mucosa. There was obvious tumor tissue extending down the length of the common duct, surrounding it completely, and extending into the region of the head of the pancreas. It was the impression, however, that the tumor nodules were lymph nodes around the head of the pancreas rather than in the pancreatic tissue and that the probabilities were all in favor of a primary carcinoma of the gall bladder that had spread to the pancreas rather than in the reverse direction. It is frequently very difficult to decide in this group of tumors which spot is primary. The tumor, extraordinarily enough, had not infiltrated the liver although it was in the lymphatics of the gall-bladder wall. Usually, carcinoma of the gall bladder invades the liver very widely and very early. In the lung the lesions were so small that they could not be picked up grossly, but microscopically the lymphatics throughout the pulmonary tissue were filled with tumor emboli.

One of the very unusual findings of the case was an obvious polyp of the endometrium, which on microscopical section showed metastatic cancer in the lymphatics within the polyp. The explanation of the central-nervous-system symptoms remains rather doubtful. I have to ask Dr Kubik to tell us what he found.

DR CHARLES S KUBIK No explanation for the cerebral symptoms has been found. Both explorations were negative for subdural hematoma,

and at the second operation the brain itself was explored, with a negative result. On post-mortem examination there were numerous ecchymoses and small extravasations of blood on the inner surface of the dura, not only near the sites of the operations but also at considerable distances from them. This is almost surely a late development, which did not account for the cerebral symptoms. The conditions were probably explained by the surgical procedures and also perhaps by a hemorrhagic tendency, for which there was considerable clinical evidence, in spite of the negative blood studies. The patient did have ecchymoses of the skin and probably a hematoma of the orbit. There was little or no flattening of the convolutions, the ventricles were not enlarged, and there were no pressure cones. Aside from the mental status, papilledema, a spinal-fluid pressure equivalent to 400 mm of water and a protein of over 100 mg per 100 cc. were very real abnormal findings, and it is remarkable that nothing was found to explain them.

DR MALLORY I neglected to mention one finding that may have had some significance. There was embedded in the ampulla of Vater a small gallstone, so that she had definite cause for obstruction in the biliary tract—two causes, both carcinoma and the gallstone. In a certain number of cases of liver disease, this type of bleeding is seen when platelets, prothrombin time and everything else are normal, nevertheless, the patient bleeds extensively.

DR ALFRED KRANES She did not have liver disease?

DR MALLORY She had extrahepatic biliary-tract disease of severe grade without, however, clinical jaundice. The liver showed only insignificant changes.

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THE MASSACHUSETTS MEDICAL SOCIETY

and

THE NEW HAMPSHIRE MEDICAL SOCIETY

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From the long-range point of view it would be more realistic to include the military deaths and the mortality among displaced persons, and to take some account of the psychiatric, moral and spiritual casualties of the past decade, but perhaps these are not germane to the subject. It is hoped that the old saw may be trusted — that when all men have sound bodies, sound minds will result.

At any rate, one cannot but agree with the American chief delegate that the United States may well increase its contribution to WHO from five to seven millions of dollars.

SHALL THE LADIES JOIN US?

MEN, by and large, have one broad outlet for ministering to the health of their fellow beings. This is the profession of medicine, with its ramifications. Women, more subtly, have various methods of accomplishing the same purpose. The first, patently, is nursing, in which they reign supreme, casting into shadow men's efforts in this field. As medical secretaries, as technicians and in the research laboratory women perform subsidiary but invaluable services.

Other ways in which the more resourceful sex can contribute to the health of the community are illustrated by two interesting letters to the editor, to be found in this issue of the *Journal*. That from Dr. Edith Varney suggests the indomitable courage with which a young woman nearly sixty years ago, emulating Trotula, Rebecca and Constanza, the medical "ladies of Salerno," became one of the notable group of women physicians of this country.

The other, from the pen of the president of the Woman's Auxiliary to the Massachusetts Medical Society, gives intimations of the way in which women have guided the affairs of nations since the world began. As Esther to Ahasuerus, so may the women of the Auxiliary further the projects of their husbands and direct them into the most fruitful channels.

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It goes without saying that England's current system of medical practice is at present undesired in this country. The present Congress recognizes the fact, even as Congress, most of the medical profession and a majority of the people believe that improvement in the quality and distribution of medical care can and must and shall be made.

The British deserve credit for being among the most reasonable people on earth, with a wholesome respect for authority, once authority has been granted. Thus with Britain's minister of health, whose insistence on the acceptance of the present Health Act by Britain's medical profession caused so much unhappiness a year ago, Mr. Bevan's authoritative utterances on matters of health are now received unquestioningly, and duly appear in the British medical press.

In the section on Medical Notes in Parliament, in the *British Medical Journal* of August 6, 1949, following a request from Mr Bevan that x-ray films be used economically, and a refusal by him to agree to a proposed transfer of the South-Western Hospital to St Thomas's Hospital, there appears a decision from the minister regarding the toxicity of ducks' eggs. Ducks' eggs, according to this statement, are eaten most safely after being baked or fried or boiled for ten minutes provided they have not been preserved in water glass.

As an example of extreme co-operation on the part of the profession, the *Lancet* of May 28 refers to the hospital surgeon who wrote on a case paper "This patient requires a hernia for his truss."

Among the 240 idiots described by the Commissioners to the Legislature of Massachusetts, 7 seem to have been made so by their mothers' trying to procure abortion by using very powerful drugs. Although these unborn children were not thus quite killed, yet they were irrecoverably stupefied and malformed to the lowest degrees of both mental and animal idiocy and weakness.

Boston M & S J, November 14, 1849

MASSACHUSETTS MEDICAL SOCIETY



DEATH

SCHOLZ — Samuel B Scholz, M D., of Jenkintown, Pennsylvania, died on March 4. He was in his seventy-second year.

Dr Scholz received his degree from Denver and Gross College of Medicine in 1905. He was medical director of the Penn Mutual Life Insurance Company of Philadelphia and was a fellow of the American College of Physicians and the American Medical Association and a retired member of the Massachusetts Medical Society.

His widow and a son survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PROJECT FOR DENTAL RESEARCH

Under the provisions of Section 1, Chapter 473, of the *General Laws* of the Commonwealth, the Department has instituted a research project, which has been approved by the Massachusetts Dental Society, to evaluate the feasibility of expanding the training of auxiliary dental personnel. Under the law, the project is limited to a period of five years,

the first two years being devoted to the training of female personnel and the last three representing an effort to determine the quantity and quality of dental service that can be rendered by auxiliary personnel to help overcome the wide disparity between dental needs and existing facilities. The project will be conducted at the Forsyth Dental Infirmary for Children. A representative group of students will be selected from the first-year class of the Forsyth School for Dental Hygienists, eventually to qualify as dental hygienists under the laws of Massachusetts.

Dr Howard M. Marjerson and Dr Charles E. Hatch, both members of the staff of the Infirmary, will be, respectively, director and clinical supervisor of the project. Dr William D. Wellock, of the Dental Division of the Department, will act as liaison officer between the Department and the Infirmary, and Dr William H. Griffin, dental director of the City of Boston Health Department and member of the State Health Department Public Health Council, is chief consultant. Other consultants appointed include leaders in dentistry and public health. In the near future, the commissioner, with the advice of the Massachusetts Dental Society and other interested groups, will appoint an advisory committee of dentists, public-health officers, social workers and other professional groups and civic leaders, to review periodically the reports of the project.

Every effort will be made to keep the dental profession informed of the progress of the project.

CORRESPONDENCE

NEVER UNDERESTIMATE THE POWER OF A WOMAN

To the Editor The following two letters, which have been in my possession for many years, may prove of interest to the readers of the *Journal*, particularly as the first women to be admitted to Harvard Medical School are entering on their final year.

Harvard University,
Cambridge, September 22, 1890

My dear Dr Bowditch,—

I regret to say that there is as yet no provision for the medical education of women either in Harvard University or by the Society for Promoting the Collegiate Education of Women. Please excuse the delay in replying to your note of September 13th. It was first forwarded to Mount Desert and then returned to Cambridge.

Very truly yours,

Dr Henry I. Bowditch

Charles W. Eliot

Peterborough
Sept. 24, 1890

Miss Varney
Dear Madam

I am not surprised at the tenor of President Eliot's reply, which I enclose. I deem the position of Harvard in regard (to) the education of women, one of which essentially the University will be thoroughly ashamed.

Even the word "Annex," which is connected with the Academic Department shows its low estimate of women. I never can think of it save with a certain contempt for the proud self-sufficiency evinced by the term. The Corporation virtually says "You women shall not join in the

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Volume 241

NOVEMBER 24, 1949

Number 21

ERYTHROBLASTOSIS FETALIS

V The Value of Blood from Female Donors for Exchange Transfusion*

FRED H ALLEN, JR., M.D.,† LOUIS K. DIAMOND, M.D.‡ AND JOSEPH B. WATROUS, JR., M.D.§

BOSTON AND NEW YORK CITY

IN reviewing the data from 208 cases of erythroblastosis fetalis treated by exchange transfusion, we were surprised to note that although the mortality was over 15 per cent in the whole group, there were no deaths in a group of 42 babies who happened to receive blood from female donors exclusively. This prompted the examination by statistical methods of available data in this large

bank records, and the sex of the donor was thus determined for almost all the babies in our series. Lately, we have been using blood from females only, but up to this time the selection of blood had been completely random as far as the specificity of sex of the donor was concerned. This report includes no cases in which female blood was selected deliberately, except for the parenthetical

TABLE 1 Relation of Outcome to Sex of Baby and of Blood Donor in 179 Babies with Erythroblastosis Treated by Exchange Transfusion*

SEX OF BABY	SEX OF BLOOD DONOR	LIVING PATIENTS		DEAD PATIENTS					SURVIVAL RATE	
		RECOVERY WITH NO SEQUELAE	SURVIVAL WITH KERNICTERUS	PATIENTS WITH KERNICTERUS	AGE AT DEATH OF PATIENTS WITHOUT KERNICTERUS					TOTALS
					0-6 hr	6-24 hr	24-72 hr	over 72 hr		
Male	Male	52	5	6	1	2	5	2	71	84 0
	Female	22	2	0	0	0	0	0	27	
	Male and female	7	0	0	1	1	0	0	9	
	Unknown	5	0	0	0	0	0	0	5	
Female	Male	34	1	1	4	2	2	2	66	86 0
	Female	14	1	0	0	0	0	0	15	
	Male and female	8	0	2	0	0	0	0	10	
	Unknown	2	0	0	0	0	0	0	2	
Totals		167	7	9	6	5	7	4	20	
Average										84 0

*Including all erythroblastic babies treated with an exchange transfusion of more than 150 cc

series, which showed that this finding has true significance.

It should first be noted that the sex of the blood donor was included in our data only as an afterthought, our interest being turned in this direction by our recent finding¹ that female babies with erythroblastosis fetalis do significantly better than male babies, especially with regard to the incidence of kernicterus. It was relatively easy to find out which donors were female by search of the blood-

statement that, since the use of blood from female donors only, we have treated 13 babies with exchange transfusion, with no deaths.

Table 1 shows the results of erythroblastosis fetalis in 205 consecutive babies, treated by the method of exchange transfusion using the umbilical vein as described by Diamond,² in which 150 cc or more of blood was given to the baby. This figure (150 cc) was picked arbitrarily, but it represents at least twice the amount that would be given in a single transfusion to a newborn baby, and certainly one could not consider that a successful exchange transfusion had been done with a smaller amount. Only 3 babies in our series were omitted from consideration in Table 1, because they received less than 150 cc of blood. One of these 3

*From the Blood Grouping Laboratory of Boston Children's Medical Center, Boston, the Boston Lying-in Hospital and the departments of Pediatrics and Obstetrics, Harvard Medical School.

†Instructor in pediatrics, Harvard Medical School; associate director of the Blood Grouping Laboratory.

‡Associate professor of pediatrics, Harvard Medical School; director of the Blood Grouping Laboratory.

§Formerly house officer in obstetrics, Boston Lying-in Hospital and associate of the Blood Grouping Laboratory.

Academic Rule because you are inferior to us, but as you want to learn something, we will have a small center connected with our University, an "Annex" and the professors, who choose to do so, are allowed to teach you in certain departments. But in this Department of Medicine in certain courses of which woman is fitter than man to practise the art—we will never teach you.

Thank Heaven! other Universities in this country and in Europe have higher ideals in regard to women.

I regret that I cannot help you, but if you think (of) any further counsel I can give you I hope you will write again.

Respectfully yours,
Henry I Bowditch

Boston University took me in, from which I graduated in the Class of 1893. I interned at what is now Massachusetts Memorial Hospitals from January 1894 to 1895, then went abroad and spent a year studying at Vienna and other medical centers. I practiced in Lynn for fifty years, retiring four years ago.

EDITH C VARNEY, M.D.
Newfields, New Hampshire

ORGANIZED HELPMATES

To the Editor: A well known physician telephoned me recently to solicit aid from the Woman's Auxiliary to the Massachusetts Medical Society in a particular matter. As a result of the conversation I was sure that this doctor had no idea who made up the membership of the Auxiliary, and what its objectives are.

Perhaps other *Journal* readers are unaware that there has been a national organization of doctors' wives since 1922, and that this society grew from a small reception to physicians' wives at the home of Dr. McReynolds of Dallas, Texas. In 1917 while Mrs. McReynolds was greeting a guest she asked her how she liked Dallas. The guest replied "I like Dallas very much. I have lived here for thirty years."

The wife or widow of any fellow in good standing in the Massachusetts Medical Society, who is not herself a physician and a fellow, is eligible for membership in her own district. We have a comprehensive twenty-point program and hope, with the help of our medical advisers, to have the whole state fully organized by 1950. Massachusetts has been far behind the other states in forming an auxiliary, but in our first year, under the leadership of Mrs. Leighton Johnson, we acquired a thousand members.

My message to the fellows of the Massachusetts Medical Society is "Doctor, does your wife belong?"

ELIZABETH C AYERS, President
Woman's Auxiliary to the
Massachusetts Medical Society

Worcester, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The 1948 Year Book of Endocrinology, Metabolism and Nutrition Endocrinology Edited by Willard O Thompson, M.D., clinical professor of medicine, University of Illinois College of Medicine, attending physician (senior staff), Henrotin Hospital, and attending physician, Grant Hospital of Chicago. *Metabolism and Nutrition* Edited by Tom D Spies, M.D., chairman, Department of Nutrition and Metabolism, Northwestern University School of Medicine, and director, Nutrition Clinic, Hillman Hospital, Birmingham, Alabama. 16°, cloth, 544 pp., with 87 illustrations. Chicago Year Book Publishers, Incorporated, 1949. \$4.50.

Contribución de la vitamina K a la terapéutica de la alergia By Dr. E. F. Llovet. 12°, paper, 85 pp. Montevideo Editorial "Montevideo," 1949.

Haematologica Archivio Vol 32, 1948. 8°, paper, 508 pp. Pavia Tip "La Bodoniana," 1948.

Le Trincee Cliniche Della Tonsillectomia By Guido Calderoli. 8°, paper, 78 pp. Bergamo, Italy F. LLI Carrara, 1948.

NOTICES

ANNOUNCEMENTS

Dr. Robert H. McCarter announces the opening of an office at 65 Bay State Road, Boston, for the practice of psychiatry.

Dr. Irving H. Steinberg announces the opening of his office for the practice of internal medicine at 146 Chestnut Street, Springfield.

NEW ENGLAND CONFERENCES ON ALLERGY AND RELATED SUBJECTS

A number of programs on allergy and related subjects, open without charge to all interested, is planned for the coming year. These are to be presented under the auspices of the Department of Medicine of Boston University School of Medicine, Courses for Graduates, Harvard Medical School, and the Postgraduate Division, Tufts College Medical School.

The first meeting will take place on Wednesday afternoon and evening, November 30. The afternoon program, consisting of the presentation and discussion of cases with special emphasis on the use of the antihistaminic drugs, will be held in the lower Out Patient Department amphitheater of the Massachusetts General Hospital, Fruit Street, Boston, from 3:00 to 5:00 o'clock.

The evening program will take place in the Sheraton Room of the Copley Plaza Hotel, Copley Square, Boston, at 8:30 o'clock. Dr. Earl R. Loew will speak on the subject "The Role of Histamine in Anaphylaxis and Allergy in the Light of Experience with the Antihistaminic Drugs."

All members of the medical profession are cordially invited to both the afternoon and the evening meetings.

NEW ENGLAND PEDIATRIC SOCIETY

The next meeting of the New England Pediatric Society will be held in Boston on Wednesday, December 7.

The afternoon and evening meeting will be devoted to a discussion of ACTH.

A detailed program will be published at a later date.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The December and January meetings of the New England Society of Anesthesiologists will be as follows:

A regular meeting will be held in the Auditorium of Building A, Boston University School of Medicine, Boston, on Tuesday, December 13, at 8 p.m. Dr. Emanuel M. Papper, executive officer and professor, Department of Anesthesia, Columbia—Presbyterian Medical Center, New York City, will speak on the subject "Diagnostic and Therapeutic Nerve Blocks."

A regular meeting will be held in the Auditorium of Building A, Boston University School of Medicine, Boston, on Tuesday, January 10, at 8 p.m. Dr. Edward F. Bland will speak on the subject "The Appraisal and Preparation of Poor Risk Patients for Surgery."

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The ninth lecture will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Thursday, December 15, at 8 p.m.

Dr. Eugene R. Sullivan will speak on the subject "Crush Syndrome and Related Conditions."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will be shown during this period.

(Notices concluded on page xv)

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FRED H ALLEN, JR, M D,† LOUIS K DIAMOND, M D,‡ AND JOSEPH B WATROUS, JR, M D§

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IN reviewing the data from 208 cases of erythroblastosis fetalis treated by exchange transfusion, we were surprised to note that although the mortality was over 15 per cent in the whole group, there were no deaths in a group of 42 babies who happened to receive blood from female donors exclusively. This prompted the examination by statistical methods of available data in this large

bank records, and the sex of the donor was thus determined for almost all the babies in our series. Lately, we have been using blood from females only, but up to this time the selection of blood had been completely random as far as the specificity of sex of the donor was concerned. This report includes no cases in which female blood was selected deliberately, except for the parenthetical

TABLE 1 Relation of Outcome to Sex of Baby and of Blood Donor in 179 Babies with Erythroblastosis Treated by Exchange Transfusion *

SEX OF BABY	SEX OF BLOOD DONOR	LIVING PATIENTS		DEAD PATIENTS				TOTALS	SURVIVAL RATE	
		RECOVERY WITH NO SEQUELAE	SURVIVAL WITH KERNICTERUS	PATIENTS WITH KERNIC TERUS	AGE AT DEATH OF PATIENTS WITHOUT KERNICTERUS					
					0-6 hr	6-24 hr	24-72 hr	over 72 hr		
Male	Male	52	3	6	1	2	5	2	71	84 0
	Female	23	2	0	0	0	0	0	27	
	Male and female	7	0	0	1	1	0	0	9	
	Unknown	5	0	0	0	0	0	0	5	
Female	Male	54	1	1	4	2	2	2	66	86 0
	Female	14	1	0	0	0	0	0	15	
	Male and female	8	0	2	0	0	0	0	10	
	Unknown	2	0	0	0	0	0	0	2	
Totals		167	7	9	6	5	7	4	205	
Average										84 9

*Including all erythroblastotic babies treated with an exchange transfusion of more than 150 cc.

series, which showed that this finding has true significance.

It should first be noted that the sex of the blood donor was included in our data only as an afterthought, our interest being turned in this direction by our recent finding¹ that female babies with erythroblastosis fetalis do significantly better than male babies, especially with regard to the incidence of kernicterus. It was relatively easy to find out which donors were female by search of the blood-

statement that, since the use of blood from female donors only, we have treated 13 babies with exchange transfusion, with no deaths.

Table 1 shows the results of erythroblastosis fetalis in 205 consecutive babies, treated by the method of exchange transfusion using the umbilical vein as described by Diamond,² in which 150 cc or more of blood was given to the baby. This figure (150 cc) was picked arbitrarily, but it represents at least twice the amount that would be given in a single transfusion to a newborn baby, and certainly one could not consider that a successful exchange transfusion had been done with a smaller amount. Only 3 babies in our series were omitted from consideration in Table 1, because they received less than 150 cc of blood. One of these 3

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died In each case the donor was male Table 1 shows little difference in outcome dependent on the sex of the baby, and this point is discussed further

Table 2, the figures for which are taken from Table 1, shows the significance of the apparent benefit from use of blood from female donors

TABLE 2 Relation of Mortality to Sex of Blood Donor *

SEX OF DONOR	OUTCOME		SURVIVAL RATE
	SURVIVAL	DEATH	
		TOTALS	%
Female	42	0	100 0
Male	110	27	80 3
Totals	152	27	
Average		179	85 0

* $\chi^2 = 9.73$

χ^2 for these data is 9.73 (A statistically significant value for χ^2 in a table of this sort [2 x 2 table] is 3.84) The probability of obtaining a larger value than 9.73 for χ^2 (that is, the likelihood of obtaining a similarly striking difference in mortality in a

TABLE 3 Relation of Mortality to Sex of Blood Donor *

SEX OF DONOR	OUTCOME		SURVIVAL RATE
	SURVIVAL	DEATH	
		TOTALS	%
Female plus male and female	57	4	93 5
Male plus unknown	117	27	81 3
Totals	174	31	
Average		205	84 9

* $\chi^2 = 4.94$

comparable series of cases), by chance alone, is less than 1/100, though somewhat greater than 1/1000

In Table 3 is shown an unsuccessful attempt to discredit the value of blood from female donors

TABLE 4 Relation of Sex of Donor to Sex of Baby, and Outcome of Erythroblastosis Fetalis *

SEX OF BABY AND DONOR	LIVING BABIES	DEAD BABIES	TOTALS	SURVIVAL RATE
				%
Female baby, female donor	15	0	15	100 0
Male baby, male donor	55	16	71	77 5
Totals	70	16	86	

* $\chi^2 = 2.80$

Babies who received blood from female donors are compared with all the others This is probably unfair, since in cases in which blood from both male and female donors was used there was no note on the record to indicate which blood was used first and then washed out by the other blood χ^2 (4.94) for the data in Table 3 is still statistically significant,

since a figure of this value would occur less than once in 20 times by chance alone

Since, as previously reported,¹ the sex of the infant has an important effect on mortality this was next analyzed with relation to the sex of the donor whose blood was used In Table 4, the mortality in male babies receiving blood from male donors is seen to be 22.5 per cent as compared to no mortality in the female babies receiving blood from female donors With Yates's correction for small series, χ^2 for the data in Table 4 is only 2.80, which is not significant However, when this is added to the similar χ^2 for Table 5, a significant

TABLE 5 Further Data on Relation of Sex of Blood Donor to Sex of Baby, and Outcome of Erythroblastosis Fetalis *

SEX OF BABY AND DONOR	LIVING BABIES	DEAD BABIES	TOTALS	SURVIVAL RATE
				%
Female baby, male donor	55	11	66	83 4
Male baby, female donor	27	0	27	100 0
Totals	82	11	93	

* $\chi^2 = 3.63$

χ^2 is obtained — 6.43 for two degrees of freedom Table 5 shows a mortality of 16.5 per cent in female babies receiving blood from male donors, as compared with no mortality in the 27 male infants receiving blood from female donors χ^2 for Table 5 is a figure approaching statistical significance, which is of particular importance so far as the value of blood from female donors is concerned when

TABLE 6 Chance Distribution of Male and Female Donors According to the Sex of the Baby in 179 Cases of Erythroblastosis Fetalis *

SEX OF BABY	MALE DONORS	FEMALE DONORS	TOTALS	PERCENTAGE OF FEMALES
				%
Male	71	27	98	27 6
Female	66	15	81	18 5
Totals	137	42	179	

* $\chi^2 = 2.01$

compared with previous data¹ indicating the relatively favorable prognosis for female babies Table 6 indicates a chance tendency (not statistically significant) to select blood from female donors for transfusion of male babies in this series This may account in part for the generally more favorable outcome in male infants in our series than would have been expected on the basis of our earlier reports Also on the basis of this previous experience, we have thus selected, by chance, a group of babies with somewhat less favorable prognosis in which to use blood from female donors This increases the value of the data in Table 2

The remainder of the statistical analysis considers only the 179 babies included in Table 2, cases in which the sex of the donor could not be ascertained or in which bloods from both male and female donors were used being eliminated. The data in Table 7 and 8 demonstrate that no other factors, chance or otherwise, can be held responsible for the benefit of blood from female donors. Table 7 and 8 compare the results, based on the sex of the blood donor, with the severity of illness, the infant's red-cell count, the mother's titer, the ratio between mother's titer and baby's titer, the length of gestation, the amount of blood given, the baby's age when the transfusion was started, the age of the blood used and, finally, the chronological period.

First, the figures for severity of disease at birth (Table 7 and 8) indicate that more than chance selection was involved in the giving of blood from

sicker babies are considered, the beneficial effect of blood from female donors is still striking, χ^2 being 4.58 (Table 8). The significant selection of blood from male donors for sicker babies does not, therefore, discredit the use of the female donor.

Since the severity of erythroblastosis fetalis is not easy to judge in the newborn baby, since in our series some babies were considered "sick" because of intrauterine anoxia or atelectasis even though the red-cell count was high and since in some babies with low red-cell counts the disease was considered "mild" because of their excellent condition otherwise, it was thought desirable to analyze for other data involved in the determination of "severity of disease." Eight other tables similar to Table 7 were made, and the essential information from them is presented in Table 8, with the essential data from Table 1 and 7 included for comparison. Analysis of the red-cell count at

TABLE 7 *Relation of Severity of Disease at Birth to Outcome in 179 Cases of Erythroblastosis Fetalis*

DEGREE OF DISEASE AT BIRTH	SEX OF BLOOD DONOR	LIVING PATIENTS		PATIENTS WITH KERNICTERUS	DEAD PATIENTS				TOTALS	SURVIVAL RATE
		RECOVERY WITH NO SEQUELAE	SURVIVAL WITH KERNICTERUS		AGE AT DEATH OF PATIENTS WITHOUT KERNICTERUS					
					0-6 hr	6-24 hr	24-72 hr	over 72 hr		
None	Male	20	1	1	0	0	1	0	22	93.9
	Female	9	1	0	0	0	0	0	10	
Mild	Male	38	2	0	1	0	1	0	42	96.7
	Female	18	0	0	0	0	0	0	18	
Moderate	Male	52	1	5	1	0	0	2	59	87.8
	Female	9	1	0	0	0	0	0	10	
Severe	Male	16	0	5	5	4	5	2	22	54.0
	Female	5	1	0	0	0	0	0	4	
Totals		145	7	7	5	4	7	4	179	85.0
Average										

female donors to a larger percentage of mildly affected babies than to the sicker babies, and it is believed that there was a greater tendency to select bloods with higher packed cell volume (almost invariably from male donors) when the baby was very sick. A tabulation of donors by sex in the two blood banks from which most of the blood was obtained shows that in one bank (Boston Lying-in Hospital), where blood from female donors constitutes about 28 per cent of the total, such blood was chosen in only 22 per cent of the cases, and at the other bank (Children's Medical Center), where blood from female donors constitutes about 24 per cent of the total, it was chosen in only 21 per cent of the cases. This confirms our recollection of having chosen bloods with higher cell volume when other factors (amount and freshness) were equal. The selection of blood from male donors for "sicker" babies has statistical significance, χ^2 being 4.76, and it obviously decreases the value of the data in Table 2. However, when only the

or shortly after birth shows again a significant (χ^2 of 4.64) tendency to use blood from male donors for sicker babies. Again, however, the beneficial effect of blood from female donors is most striking in the group of babies with low red-cell counts, the χ^2 of 3.75 being on the borderline of statistical significance.

When the mother's anti-Rh titer is taken into account (Table 8) there is again a tendency (not statistically significant) to use blood from male donors for babies who would be expected to have more serious disease (born to mothers with high titers).² The ratio of mother's titer to baby's titer, which has been found to have a closer statistical relation to prognosis than the baby's titer alone,¹ was next considered. The figures show no tendency to selection of blood from male donors for babies with worse prognosis (Table 8).

There is known to be a highly significant relation between immaturity (gestation of less than thirty-eight weeks) of the baby and an unfavorable prog-

nosis in erythroblastosis fetalis.³ Table 8 shows a chance tendency (χ^2 of 3.58 not quite significant statistically) to use blood from female donors for immature babies. This partly balances the statistically unfortunate tendency to use blood from

others with siblings with erythroblastosis or with mothers given transfusions of Rh+ blood, 8 died, and of 60 with no history of erythroblastosis fetalis among siblings or transfusion of Rh+ blood in the mother, 12 died. There is thus no

TABLE 8 Consolidated Statistical Data

CLINICAL DATUM	CLASSIFICATION	SURVIVAL %	MALE DONORS	FEMALE DONORS	PERCENT- AGE OF FEMALE DONORS	SURVIVAL ACCORDING TO SEX OF DONOR		
						MALE DONOR %	FEMALE DONOR %	χ^2
All babies receiving blood from donor or donors of one sex (179 cases)†		85.0	137	42	23.4	80.3	100	9.73
Severity of disease at birth‡	None or mild	95.8	65	28	30.1	93.9	100	0.61
	Moderate or severe	73.3	72	14	16.3	68.0	100	4.58
Baby's red-cell count	Over 3,000,000	95.1	55	26	32.1	92.8	100	0.63
	3,000,000 or less	73.3	59	12	16.9	67.8	100	3.75
Mother's titer	Less than 1:64	84.7	66	25	27.5	78.8	100	4.74
	1:64 or higher	81.9	54	12	18.2	77.8	100	1.93
Ratio of mother's titer to baby's titer	1-8	87.0	64	20	23.8	83.0	100	2.60
	16 or higher	79.5	56	17	23.3	73.3	100	4.20
Length of gestation	38 wk. or longer	89.2	97	23	19.2	86.7	100	2.21
	Less than 38 wk.	75.0	38	18	32.2	63.2	100	6.98
Amount of blood given	400-500 cc.	91.3	70	23	24.7	88.5	100	1.59
	All other	78.0	67	19	22.1	71.8	100	5.35
Age when started	Over 3 hr.	86.5	56	18	24.3	82.2	100	2.34
	3 hr. or less	84.2	77	24	23.7	79.3	100	4.47
Age of blood	0-9 days	86.1	87	28	24.3	81.7	100	4.54
	Over 9 days	84.7	41	11	21.1	80.5	100	1.25
Chronologic period	Since 3/11/48	87.5	69	19	21.6	84.1	100	2.13
	Before 3/11/48	82.5	68	23	25.3	76.5	100	5.04

* χ^2 was calculated in each case from 2 x 2 tables similar to Table 2.

†Table 1 was source of data.

‡Table 7 was source of data.

male donors in babies with unfavorable signs and symptoms at birth.

Analysis of the amount of blood given, the age of the baby when the transfusion was started and the chronologic period (Table 8) shows no tendency to use blood from male donors more frequently in the groups with higher mortality, but in each case there was a significant (by χ^2) benefit from blood from female donors in the groups with higher mortality. No significant differences in mortality dependent on the age of the bank blood could be shown (Table 8). Table 9 shows no significant relation between sex of donor and the later need for additional small transfusion in babies having an exchange transfusion, although the percentage is somewhat higher in the group of cases in which blood from female donors was used.

Table 10 gives the most important clinical and laboratory data available in babies treated by exchange transfusion of blood from female donors. In 11 cases there was a previous death from erythroblastosis fetalis, and in an additional 9 there was an erythroblastotic baby or a transfusion of Rh+ blood at some time in the mother's past history. Both these factors have been shown² to have serious implications toward the survival of later infants. The comparable figures for babies receiving blood from male donors are as follows: of 37 with siblings dying of erythroblastosis, 7 died, of 40

significant difference in the two groups with respect to the past history. The table is arranged in order of severity as judged by the red-cell count. It can be seen that, although there is a distinct tendency to milder anemia in this group as compared with the group receiving blood from male donors,

TABLE 9 Relation of Sex of Blood Donor to Need for Later Transfusions in 152 Babies Receiving Exchange Transfusion during the First Day of Life

LATER TRANSFUSION NECESSARY AFTER EXCHANGE TRANSFUSION	SEX OF BLOOD DONOR	LIVING INFANTS		TOTALS
		RECOVERY, WITH SEQUELAE	SURVIVAL, WITH KERNICTERUS	
Yes	Male	15	1	16
	Female	8	1	9
No	Male	86	3	89
	Female	28	2	30
Unknown	Male	5	0	5
	Female	3	0	3
Totals		145	7	152


there is included a fair number of babies with marked anemia, and a few were desperately sick. Infant B41343 was very pale, edematous and limp, with grunting respirations and a tense and bulging abdomen. The hemoglobin was measured at 7.5 gm, and the red-cell count at 770,000 at birth.

Jaundice became marked in this baby, but he did "amazingly well" after transfusion. This has been considered as a case of kernicterus because the patient is stone deaf, but he seems to be alert and has no apparent motor handicap, which makes one seriously question the diagnosis of kernicterus. Infant R12348 was pallid, limp and edematous, with marked hepatosplenomegaly. The red-cell count was 1,550,000 at birth. These 2 cases can be truly classified as hydrops fetalis. Several other babies were very sick, with asphyxia or atelectasis. Considering the fact that about 50 per cent of our patients are referred because of previous trouble and that all were *selected* for exchange transfusion, this group of 42 infants probably represents a considerably more severe degree of erythroblastosis than would be found in a true cross-section of the population. Some, with high red-cell counts at birth, received exchange transfusion because of the finding of circulating antibodies in the baby's blood, and the same statement is true for a similar proportion of the group receiving blood from male donors. We no longer consider the presence of circulating antibodies a criterion for exchange transfusion, since we have found this qualitative determination to have relatively little value in prognosis. Some infants in each group had an exchange transfusion in spite of a relatively high red-cell count because of a titer of 1:64 or higher in the mother's serum, determined prior to delivery. This is a better criterion. Others received exchange transfusion because of the rapid development of jaundice, or the presence of unusual hepatosplenomegaly. A very few babies were treated with exchange transfusion solely on the basis of an unusually unfavorable past history of stillbirths or deaths from erythroblastosis.

In our previous studies the most striking sex difference was the marked relative infrequency of kernicterus in female babies. This was the observation that suggested the possible value of investigating the sex of the donor. Because Vaughan et al.⁴ had been able to demonstrate that kernicterus is an *acute* disease of the neonatal period and therefore theoretically preventable, it was hoped that the incidence of kernicterus might have been lower when blood from female donors was used for transfusion. Such a hope, however, was not borne out, according to the figures obtained from this analysis. Table 11 shows a 7.2 per cent incidence of kernicterus in the group of babies receiving blood from female donors, as compared with 8 per cent, an almost identical figure, in the group receiving blood from male donors. This is most disappointing, but is probably important evidence in the study of kernicterus. It is still more disappointing to note that all 3 babies with kernicterus who received blood from female donors survived. This does not constitute convincing statistical evidence that the survival of babies with kernicterus

is greater with the use of blood from female donors (the incidence of kernicterus is only about 7 per cent), but it is difficult to escape the conclusion that the use of such blood may save more of these badly damaged babies, whose prompt death has in the past so mercifully ended their problems in the great majority of cases.

EFFECT OF SMALL TRANSFUSIONS OF BLOOD FROM FEMALE DONORS

In an effort to ascertain the quantitative factors involved in the use of blood from female donors, an analysis was made of 200 infants with erythroblastosis fetalis who did not have an exchange transfusion but who did receive small transfusions of blood during the first day or first two or three days of life. In this preliminary survey, no beneficial effect of blood from female donors was seen for amounts up to 100 cc, so that one can say tentatively that a fair quantity of such blood must be given if its life-saving property is to be effective. This can be safely accomplished in the really sick infants only by exchange transfusion. 

DISCUSSION

It seems obvious that whatever the beneficial component of blood from female donors as far as erythroblastosis is concerned, it must be shared by virtually all young adult females, since otherwise one would not expect so striking an effect from more or less random bloods. It is true that all the donors were adult, and very few were over forty years of age (of the 42 donors, 1 was forty-two, 2 were fifty-three, and 1 was fifty-seven years of age). None were pregnant, none had recently delivered a baby, and none had ever had a baby with erythroblastosis. All were in good health so far as known.

Since it has been advised by some that the blood of the mother may be used with benefit for transfusion of the baby with erythroblastosis fetalis, particularly if one removes the antibody-containing plasma, it should be noted that in no case in our series was this performed. The time in the menstrual cycle at which the blood was taken has not been ascertained, but is a point of interest that deserves investigation, although no information of statistical value could be obtained from our material, simply because all the babies who received blood from female donors did well.

The beneficial effect of blood from female donors has been shown to result only from the use of relatively large quantities. This suggests the presence of a factor, in rather dilute form in most specimens of such blood, that might be concentrated and more active in one of the fractionation products now available for trial. Obviously, the screening of fractions that might be assumed to have no value, such as purified albumin, gamma globulin and fibrinogen, cannot be done on sick patients. The

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	16 or higher	79.5	56	17	23.3	73.3	100	4.20
Length of gestation	38 wk. or longer	89.2	97	23	19.2	86.7	100	2.21
	Less than 38 wk.	75.0	38	18	32.2	63.2	100	6.98
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is greater with the use of blood from female donors (the incidence of kernicterus is only about 7 per cent), but it is difficult to escape the conclusion that the use of such blood may save more of these badly damaged babies, whose prompt death has in the past so mercifully ended their problems in the great majority of cases.

EFFECT OF SMALL TRANSFUSIONS OF BLOOD FROM FEMALE DONORS

In an effort to ascertain the quantitative factors involved in the use of blood from female donors, an analysis was made of 200 infants with erythroblastosis fetalis who did not have an exchange transfusion but who did receive small transfusions of blood during the first day or first two or three days of life. In this preliminary survey, no beneficial effect of blood from female donors was seen for amounts up to 100 cc, so that one can say tentatively that a fair quantity of such blood must be given if its life-saving property is to be effective. This can be safely accomplished in the really sick infants only by exchange transfusion. 

DISCUSSION

It seems obvious that whatever the beneficial component of blood from female donors as far as erythroblastosis is concerned, it must be shared by virtually all young adult females, since otherwise one would not expect so striking an effect from more or less random bloods. It is true that all the donors were adult, and very few were over forty years of age (of the 42 donors, 1 was forty-two, 2 were fifty-three, and 1 was fifty-seven years of age). None were pregnant, none had recently delivered a baby, and none had ever had a baby with erythroblastosis. All were in good health so far as known.

Since it has been advised by some that the blood of the mother may be used with benefit for transfusion of the baby with erythroblastosis fetalis, particularly if one removes the antibody-containing plasma, it should be noted that in no case in our series was this performed. The time in the menstrual cycle at which the blood was taken has not been ascertained, but is a point of interest that deserves investigation, although no information of statistical value could be obtained from our material, simply because all the babies who received blood from female donors did well.

The beneficial effect of blood from female donors has been shown to result only from the use of relatively large quantities. This suggests the presence of a factor, in rather dilute form in most specimens of such blood, that might be concentrated and more active in one of the fractionation products now available for trial. Obviously, the screening of fractions that might be assumed to have no value, such as purified albumin, gamma globulin and fibrinogen, cannot be done on sick patients. The

TABLE 10 *Clinical and Laboratory Data in 42 Cases of Erythroblastosis Fetalis in Which Exchange Transfusion Was Done with Blood from Female Donors (All Babies Lived)*

RECORD No	DATE OF BIRTH	PAST HISTORY OF MOTHER (KNOWN RH NEGATIVE BABIES NOT INCLUDED)	MOTHER'S TITER	PERIOD OF GESTATION	SEX OF BABY	BABY'S TITER
B41343	4/14/47	1 normal child, 4 died with kernicterus, 1 miscarriage	1 128	36	M	1 4
R12348	6/4/47	1 normal child 1 infant with erythroblastosis fetalisis (died) 1 stillbirth	1 64	38	M	1 4
345832	5/31/49	1 miscarriage	1 64	43	M	0
317760	5/12/47	1 miscarriage 1 normal child	1 32	37	M	1 2
B41150	10/7/48	1 normal child 1 infant with erythroblastosis fetalisis (recovered)	1 32	37	M	1 2
B36909	2/8/47	2 normal children, 1 stillbirth 1 infant with erythroblastosis fetalisis (recovered) 1 infant died with kernicterus	1 16	37	M	1 4
345200	5/23/49	3 normal children 1 infant died with kernicterus	1 2	37	M	0
329770	4/16/48	1 normal child 1 miscarriage	1 16	38	M	1 16
345802	5/20/49	2 normal children (transfusion)	1 64	40	M	1 4
B26233	4/5/49	2 normal children	1 64	35	M	0
N99644	9/16/47	1 normal child 1 infant with erythroblastosis fetalisis (recovered)	1 32	37	F	1 2
B42537	11/18/46	1 normal child 1 infant died with erythroblastosis fetalisis	1 16	37	F	1 2
312348	11/29/46	1 normal child, 2 miscarriages 1 infant died with kernicterus	1 32	38	F	—
315105	2/5/47	2 normal children	1 256	36	M	1 8
347485	7/16/49	1 normal child	1 64	38	M	1 64
R21260	3/10/48	1 normal child 1 infant with erythroblastosis (recovered)	1 16	38	M	1 4
R20246	12/23/47	1 child (without erythroblastosis fetalisis)	1 16	37	F	1 2
330685	4/26/48	1 normal child	1 16	38	M	1 4
329357	3/17/48	2 normal children	1 16	41	M	0
330748	5/12/48	1 infant with erythroblastosis fetalisis?	1 16	37	M	1 1
327640	1/14/48	1 normal child 1 stillbirth	1 128	37	M	1 4
338024	10/21/48	2 normal children 1 infant with erythroblastosis fetalisis (recovered)	1 16	38	M	0
phh	3/9/47	6 normal children 1 miscarriage 1 stillbirth	1 16	37	F	0
319325	5/29/47	2 normal children 1 infant with erythroblastosis fetalisis (recovered)	1 32	40	F	1 16
316260	4/14/47	3 normal children	1 64	40	F	1 1
R18504	4/14/48	1 normal child	1 128	38	F	1 32
329146	2/24/48	2 normal children	1 32	40	F	1 16
B42484	10/26/48	1 normal child	1 16	37	F	1 1
325723	12/2/47	3 normal children 1 infant died with erythroblastosis fetalisis	1 16	41	M	1 8
R23885	5/31/49	1 normal child 2 infants died with kernicterus 1 miscarriage	1 4	38	F	1 4
315151	2/12/47	1 normal child	1 16	38	M	1 2
345077	5/6/49	2 normal children, 1 infant with erythroblastosis fetalisis and kernicterus	1 64	38	F	1 2
mmhs	5/1/47	1 normal child	1 16	37	M	1 4
R16622	7/20/48	1 child (without erythroblastosis fetalisis)	1 64	39	M	1 1
N94194	12/22/46	1 infant (without erythroblastosis fetalisis) 2 normal children	1 64	37	M	1 4
B37574	4/23/47	2 normal children	1 64	36	M	1 1
R20196	12/23/47	1 normal child 1 infant died with kernicterus	1 32	38	F	1 4
329751	4/10/48	1 normal child 1 infant (without erythroblastosis fetalisis)	1 64	40	F	1 64
R20829	6/21/47	1 normal child 1 infant with erythroblastosis fetalisis?	1 64	40	M	1 32
R16330	12/6/48	1 normal child	1 64	—	M	1 1
341763	2/11/49	1 normal child	1 4†	40	F	1 1
N94737	1/17/47	1 normal child	1 64	36	M	1 8

*This is considered to be a case of kernicterus although the absence of motor handicap throws considerable doubt on this diagnosis

†After 50-cc. transfusion

‡Hyperimmune, anti-A agglutinin

§The Coombs test has regularly been negative in our hands when anti-A or anti-B is involved

TABLE 10 (Concluded)

RECORD No	COOMBS TEST	RED CELL COUNT AT OR SHORTLY AFTER BIRTH $\times 10^6$	HEPATO- SPLENO-MEGALY	JAUNDICE	EXCHANGE TRANSFUSION		REMARKS
					IN cc	OUT cc	
B41343	—	0 77	+++	++++	975	910	Infant pallid limp edematous at birth is completely deaf*
R12348	—	1 55	++++	++++	700	610	Infant pallid limp and edematous at birth
345832	++++	1 94	+++	++++	295	295	—
317760	—	2 00	++	++++	590	535	—
B41150	++++	2 10	+++	+++	420	405	Atelectasis
B36909	—	2 10	++++	++++	445	425	Slight edema at birth kernicterus
345200	++++	2 28	+++	+++	465	500	—
329770	++++	2 45	++	++	490	475	—
345802	++++	2 48	+++	+++	475	485	Knot in cord slight meconium staining of vernix
B26233	+++	2 78	+++	++++	400	410	Infant delivered by cesarean section (because of placenta previa)
N99644	—	2 86	—	—	500	480	Spontaneous pneumothorax
B42537	—	2 90†	+++	+++	410	340	Infant very pale at birth
312348	—	2 90	++++	++++	500	400	"Sick baby"
315 05	—	—	++	+++	455	430	Slight edema at birth
347485	++++	3 10	+	+++	360	380	Marked atelectasis
R21260	++++	3 15	+	+++	315	305	—
R20246	++++	3 28	+	—	400	365	—
330685	++++	3 40	++	++++	460	445	Infant limp and pale with severe asphyxia
329357	++++	—	++	+++	530	505	—
350748	++++	3 48	++	+++	550	515	—
327640	—	3 50	++	+++	175	113	Technical failure of exchange transfusion
338024	++++	3 62	+	+++	450	430	—
pkk	—	3 70	—	+++	400	375	—
319325	—	3 73	++	+++	490	450	—
316260	—	3 75	+++	+++	500	450	—
R18504	++++	3 75	++	+++	290	270	—
329146	—	3 80	+++	+++	330	265	—
B42484	++++	4 04	+++	+++	430	420	—
325723	—	4 09	++	+++	565	535	—
R23885	++++	4 17	0	0	460	420	Late anemia
315151	—	4 33	++	+++	410	400	—
345077	++++	4 40	+	+++	495	510	—
wmhj	—	4 50	+	—	425	405	—
R16622	++++	4 60	++	++	455	395	Slight edema yellow vernix.
N94194	—	4 65	+	+++	465	415	—
B37574	—	4 76	++	+++	655	615	Slight edema
R20196	++++	4 80	+	+++	425	375	—
329751	++++	4 85	+	+++	510	470	—
R20829	—	4 95	—	—	500	445	—
R16330	++++	5 00	+	+++	150	100	—
441763	0†	5 70	+	+++	440	390	kernicterus
N94737	—	6 70	0	0	290	265	No clinical signs of erythroblastosis fetalis

more promising fractions are to be investigated as rapidly as possible. Meanwhile, it appears certain that exchange transfusion using blood from a female donor is the treatment of choice for babies with erythroblastosis fetalis. In the past two months we have deliberately given this type of blood by exchange transfusion to 13 babies with erythroblastosis fetalis. All have recovered.

Whereas all babies given blood from female donors only survived, it is equally true that all the deaths occurred in babies who received blood

potential value of a beneficial component of blood from female donors may not be limited to babies with erythroblastosis fetalis, and our preliminary study of other groups of babies requiring and receiving transfusion is promising.

SUMMARY

A study of 205 babies with erythroblastosis fetalis indicates beyond reasonable statistical doubt that exchange transfusion of blood from female donors results in a lower mortality than that from male donors. Of 137 babies receiving blood from male donors only, 27 died, a mortality of 19.7 per cent. Of 42 babies receiving blood from female donors only, none died.

The beneficial effect of a large amount of blood from female donors in babies with erythroblastosis fetalis is statistically very striking. In addition to the series of 179 cases in which no attention was paid at the time to the sex of the donor, 13 additional babies with erythroblastosis fetalis were deliberately treated with exchange transfusion using blood from female donors, with no deaths.

The quantitative aspect is briefly discussed. The beneficial component of such blood is not known, but isolated plasma fractions are being investigated. It appears that, for the present, exchange transfusion, using blood from a female donor, is the treatment of choice in babies with erythroblastosis fetalis.

We are indebted to Miss Jane Worcester, of the Department of Biostatistics, Harvard School of Public Health, for her helpful advice in the statistical analysis.

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TABLE 11 *Relation of Sex of Blood Donor to Incidence of Kernicterus*

SEX OF DONOR	RECOVERIES PLUS DEATHS NOT DUE TO KERNICTERUS	INFANTS WITH KERNICTERUS (LIVING PLUS DEAD)	TOTALS	INCIDENCE OF KERNICTERUS
				%
Female	39	3	42	7.15
Male	126	11	137	8.04

from male donors. The possibility that a harmful factor is present in some bloods from male donors should not be overlooked, but the evidence appears to favor the idea that the important factor is a protective substance in blood from female donors or the absence of such a substance in most bloods from male donors.

Finally, it appears impossible to save all live-born erythroblastotic babies by any method of treatment, since some are practically dead at delivery. It is possible that further statistical data will not substantiate the analysis here presented, though that seems highly unlikely from the evidence. At any rate, the beneficial effect of exchange transfusions using blood from female donors can be quickly ascertained from a brief study of current and past records in a number of clinics. It is hoped that such studies will be done. Obviously, the

FLEXOR TENDON GRAFTS IN THE HAND*

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IN CIVILIAN life, acute suppurative tenosynovitis and trauma to the joint phalanges are the most common causes of loss of flexor function in the hand. Loss of flexor function means loss of the "hook and pinch" mechanism, inability to grasp and hold objects and weakness of grasp. Improper treatment of the complications of acute suppurative tenosynovitis and trauma to flexor tendons in the hands have too often resulted in amputation of the fingers. In selected cases the grafting of tendons may restore function to the involved parts if there is normal joint function, good circulation and normal sensation. The following report describes methods that have been found useful in preventing the severe disability that may result from acute suppurative tenosynovitis and traumas that involve the flexor function in the hand.

For this study 100 cases of acute suppurative tenosynovitis, treated at the Boston City Hospital,¹ were compared with 50 cases treated since the advent of antibiotics. This comparison showed that acute suppurative tenosynovitis occurred about 60 per cent as frequently since the use of antibiotics as it did previous to antibiotics. The complications of acute suppurative tenosynovitis have also decreased in incidence but are still numerous and severe. The relative incidence of some complications is presented in Table 1.

Fingers with these complications may be salvaged if there is normal joint function, good circulation and normal sensation.

Trauma is the most common cause for flexion contractures of the hand. The trauma may be operative or nonoperative. Some of the common traumatic causes for loss of flexor function of the hand are enumerated.

Infection following severance of a flexor tendon within a sheath causes proliferation and adherence of tendon ends to nearby structures. Infection in tendons outside sheaths causes a greater amount of cicatricial attachment.

When the ends of a sutured tendon are disproportionate, with one end of small diameter and another of large diameter, the free or unsutured end of the tendon will proliferate and become attached to surrounding structures. Sutured ends of the tendon may retract, and the gap becomes filled with scar tissue. Sublimis and profundus tendons, which are sutured in the same plane, will adhere to each other, cause flexion contracture

and limited motion. A sutured tendon may become adherent to overlying, underlying or surrounding scar, with resultant flexion deformity.

GENERAL PRINCIPLES FOR TENDON GRAFTING

All scar tissue must be excised. After excision of excessive scar a large defect is covered with a pedicle graft. The use of paratenon or a thin sheet of areolar tissue helps gliding of tendons.

A tendon transplanted with paratenon glides better than one grafted without this thin areolar tissue. Paratenon is abundant about the palmaris longus tendon. One should always test the presence of the palmaris longus tendon before operation. This tendon is absent in about 20 per cent of pa-

TABLE 1 Incidence of Complications of Acute Tenosynovitis

COMPLICATION	INCIDENCE BEFORE ANTIBIOTICS	INCIDENCE SINCE ANTIBIOTICS
	%	%
Tendon atrophy	41	6
Osteomyelitis	31	12
Adhesions about tendon	10	5

tients. The palmaris longus tendon is readily seen and felt with tension as in cupping the hand.

A tendon grafted proximally in the palm functions better than one grafted proximally in a finger, which is encased in a relatively tight cylinder that will not accommodate the edema at the sutured site of the tendon. There may be necrosis at the sutured site, and the suture line may become adherent to the surrounding structures if the grafted site is in the finger.

Before operation it must be determined that passive motion in all joints of the involved finger is normal and that circulation in the finger is adequate. Sensation in the involved part is of primary consideration. A patient has little tendency to use an insensitive finger that has received a tendon graft. He prefers to substitute a finger with normal sensation.

The two annular ligaments in a finger should be preserved to prevent flexion bowing. The grafted tendon is threaded beneath these pulleys. After acute suppurative tenosynovitis, the annular ligaments are often imbedded in scar tissue and may have to be excised. In such a case a pulley can be reconstructed after tendon grafting if necessary.

Secondary repair of tendons may be performed within two months of the accident. After two

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months the severed tendon ends usually cannot be approximated, because the muscle has become contracted and fixed. When a tendon is lacerated, each end is usually traumatized for about 1 cm, so that some length of tendon must be sacrificed. Degeneration of disuse occurs in a tendon that has been nonfunctioning for several months and renders it unfit for repair. This reaction is found especially in the distal part of the tendon but not in the proximal part, which has become reattached and has been under intermittent tension.²

If there has been severance of the flexor profundus tendon distal to the proximal interphalangeal joint but with normal sublimis function, tendon grafting is probably not indicated. It is better to perform an arthrodesis of the distal joint in 30° flexion. However, in a patient whose occupation is highly specialized, a graft can be inserted within the finger itself.

An intact flexor sublimis of the ring finger can be cut from its distal attachment, withdrawn through a palmar incision and transferred to the little finger to replace a profundus tendon. The ring-finger sublimis can also be used to replace a flexor pollicis longus tendon in the thumb when tendon grafting is contraindicated or when the muscle of the flexor pollicis longus has been damaged.

Thatcher,³ Mayer⁴ and Ranshof⁵ have reconstructed tendon sheaths by using various material through the fingers to produce a gliding surface. However, paratenon and a moving tendon usually restore a good gliding mechanism.

The little finger is used very little in ordinary functions of the hand, and this finger is the most difficult in which to restore good function with a flexor tendon graft. Tendon grafting in the little finger should be attempted only in a patient whose occupation requires skilled use of this finger, such as a pianist or a typist.

OPERATIVE PRINCIPLES

After excision of scar tissue in the palm and finger, the flexor sublimis tendon is excised about 4 cm proximal to the excised proximal portion of the profundus tendon. The proximal stump of the sublimis may be sutured to the profundus tendon to give added power.

Tendons of small caliber are used for tendon grafting because they are readily vascularized without necrosis, are not constricted by the annular ligaments and will hypertrophy, if necessary. Free grafts swell at the sutured site during the early postoperative period, and pressure necrosis or adhesions of graft may occur if there is not ample space.² If the graft lies on exposed bone, paratenon should be interposed for gliding.

The palmaris longus is the most satisfactory tendon for grafting. This tendon may be obtained by two small transverse incisions in the forearm. However, it is more satisfactory to make a longitudinal incision in the forearm and excise the pal-

maris longus with a generous amount of paratenon to provide good mobilization.

The flexor sublimis tendon may be employed as a graft when both the sublimis and profundus tendons have been lacerated. The long extensor tendons of the second, third, fourth and fifth toes may be used, but they have a tendency to fray. The peroneus longus and plantaris tendons have occasionally been used.

Before a free graft is sutured to the flexor profundus tendon, the amplitude of excursion of the tendon should be determined by traction. It is futile to perform tendon grafting and expect a satisfactory range of flexion with a severely contracted flexor muscle.⁶

The tendon graft must be of proper length to ensure proper muscle balance and useful function. A graft is of proper length when it holds the finger in a neutral position, with flexor tension the same as in a normal finger.⁷

The tendon graft is sutured proximally to the profundus tendon, untreated No 3 silk with Bunnell technic being used. Usually, a portion of the paratenon that is adherent to the grafted palmaris longus tendon is carried over the sutured site. If the graft is sutured at the level of the lumbrical muscle in the palm, the sutured site may be covered with lumbrical muscle. The proximal suture site should never lie between the distal transverse palmar crease and the proximal interphalangeal crease.

The tendons in the affected finger are then exposed by a middle, lateral, longitudinal incision. The distal ends of the sublimis tendon are excised about 2 cm proximal to their insertions. When the sublimis tendon is excised too near its distal attachments, the proximal interphalangeal joint may hyperextend. This can be prevented by suturing of the distal stump of the sublimis tendon into the proximal phalanx, with this joint flexed at 10°.⁸

The profundus tendon is excised 1 cm proximal to its attachment in the distal phalanx. A small flap of bone is then raised with a chisel from the volar aspect and base of the distal phalanx. Two small drill holes are made in the bone defect. The drill holes emerge in the skin over the dorsum of the distal phalanx.

Catgut is never used for primary or secondary suture of tendons because of the danger of adhesions. However, adhesions are desirable when a tendon is grafted to the distal phalanx. For this reason, after the tendon graft has been threaded beneath the annular ligaments, a No 0 plain catgut is sutured to the end of the grafted tendon. The two strands of catgut then emerge from the core of the tendon. The strands of catgut are then threaded through the drill holes in the distal phalanx and tied over a button on the dorsum of the distal phalanx. The end of the grafted tendon now

fits snugly into the artificial groove in the bone. To reinforce the distal attachment of the grafted tendon, a mattress suture of No. 3 untreated silk is used to attach the distal end of the grafted tendon to the remnant of old profundus tendon. Using this procedure I have had no case in which the distal end of the grafted tendon has become detached.

POSTOPERATIVE TREATMENT

The postoperative treatment is the most important phase in tendon grafting. The hand and wrist are immobilized in a plaster cast for three weeks. The cast is then removed, and the button and remains of old catgut suture are simply wiped off the dorsum of the distal phalanx. When the cast

Motions of the metacarpophalangeal joint were normal. There was an operative scar over the lateral aspect of the finger. Sensation, circulation and passive flexion of all joints were normal.

At operation a longitudinal incision was made over the lateral aspect of the right middle finger. A transverse incision was made in the palm proximal to the distal transverse crease. Dense adhesions were found matting together all structures within the tendon sheath. The scarred tissue, which included sublimis and profundus tendons as far proximally as the distal third of the palm, both annular ligaments and most of the tendon sheath, was excised. The palmaris longus tendon was used for grafting in the manner described.

Ten weeks later, there was normal active flexion in all joints of the right middle finger (Fig. 1B) and normal extension in the two proximal joints, but a lack of the final 15° of extension in the distal interphalangeal joint (Fig. 1C). With flexion, some bowing of the grafted tendon was evident. However, with flexion there was good strength, and the tip of the middle finger touched the palm of the hand.

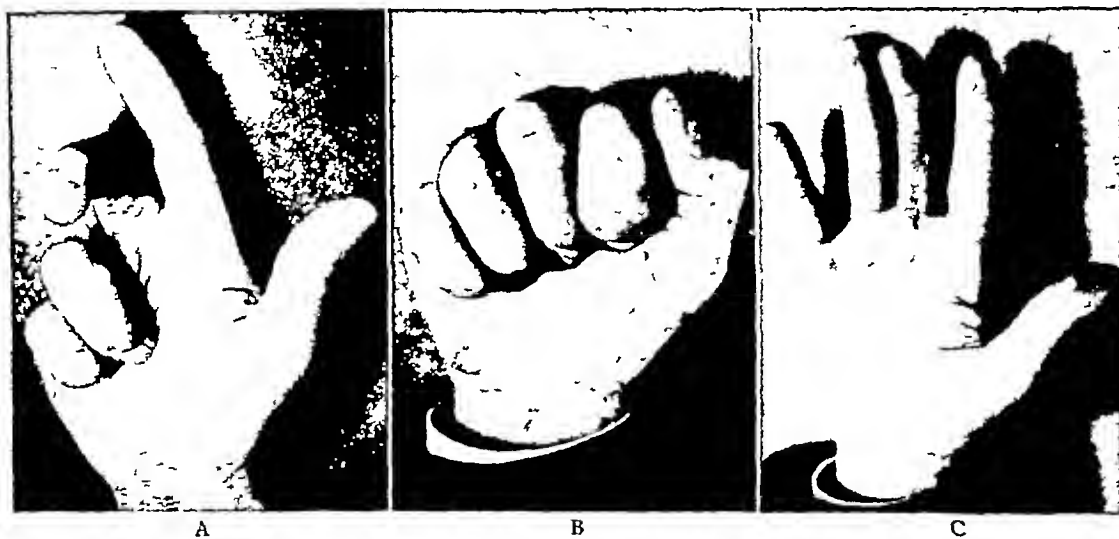


FIGURE 1 Flexion Deformity of the Right Middle Finger Due to Adhesions from a Previous Acute Suppurative Tenosynovitis (Case 1)

A shows deformity before operation, B normal flexion of right middle finger with tendon graft, and C slight bowing of grafted tendons caused by excision of the annular ligaments

is removed active motions are instituted, but care is taken not to hyperextend the fingers. After four weeks, moderately active, resistive exercises are begun, and in six weeks, flexion against resistance is encouraged. Each joint is considered individually in the forceful active flexion. Forceful but careful extension is performed after six weeks to prevent fixed flexion contractures. Occupational therapy is very helpful in restoring flexor function.

CASE REPORTS

CASE 1 A 24-year-old man had cut the volar aspect of the right middle finger with a piece of glass 1 year before entry. Acute suppurative tenosynovitis developed. Incision was performed, and the wound was drained for 3 weeks. For the past 9 months the patient had had a flexion deformity of the right middle finger.

Physical examination disclosed a flexion deformity of the right middle finger of 90° at the proximal interphalangeal joint and 15° at the distal interphalangeal joint (Fig. 1A).

In this case it may be that the reaction in the soft tissues caused by the previous infection, compensated in some degree for the loss of annular ligaments, since no pulley operation was performed.

CASE 2 A 26-year-old man had received a laceration of the palm of his left hand on broken glass 4 years previously. At the first operation the skin alone was sutured. One week later, when the patient was unable to flex his left index finger, the sublimis and profundus tendons were sutured in the palm. The left index finger was immobilized in extreme flexion for 3 weeks. Two weeks later a tendon-lengthening operation was unsuccessfully attempted in the wrist for correction of the flexion deformity, which persisted until the patient was admitted to the Veterans Administration Hospital in West Roxbury.

Physical examination revealed a scar extending from the volar aspect and proximal crease of the left index finger about 2.5 cm. proximally into the palm. This scar was adherent to the underlying flexor tendons. There was a flexion contracture of about 80° at each interphalangeal joint (Fig. 2A). Passive motions, circulation and sensation were normal.

At operation the scar was excised from the palm of the left hand. Adherent sublimis and profundus tendons and

the proximal annular ligament were excised in the palm. A pedicle graft was sutured to the defect in the palm of the left hand. Later, the sublimis tendon to the index finger was removed in the forearm and used for grafting because the palmaris longus tendon was absent.

After operation, flexion of the finger was greatly limited. Bowing of the grafted tendon was due to the loss of the an-

to the underlying flexor tendons of the middle and ring fingers. The left middle finger had the following ranges of motion: flexion of the metacarpophalangeal joint was possible 40° actively and 90° passively. Each interphalangeal joint could be flexed about 5° actively and 90° passively. In the left ring finger, flexion at the proximal joint was possible 40° actively and 90° passively. The middle and distal joints



FIGURE 2 Loss of Flexor Function Due to Adhesions between the Sutured Sites of the Sublimis and Profundus Tendons, with Adhesions in Overlying Soft Tissue but without Gross Infection (Case 2)

A shows contracture of left little finger after trauma, B bowing of grafted tendon, causing flexion of index finger, and C results of pulley operation, which aided flexion of index finger.

nular ligaments (Fig 2B). The bowing was corrected by construction of a proximal annular ligament with an extensor tendon from the lower extremity. On flexion, the tip of the index finger now reaches the palm of the hand (Fig 2C).

CASE 3 A 30-year-old dairyman fell on an icy sidewalk and cut the palm of his left hand on a broken milk bottle. The sublimis and profundus tendons to the left middle and

could be flexed 5° actively and 90° passively. Pressure from index and little fingers passively aided flexion of the middle and ring fingers (Fig 3).

The extensive scarring in the palm, including the profundus and sublimis tendons to the left middle and ring



FIGURE 3 Loss of Flexion of Middle and Ring Fingers Following Trauma and Sepsis before Operation (Case 3)

ring fingers were sutured within 2 hours of the accident. The palmar wound became septic and drained pus for 4 weeks.

On entry, 5 months after the accident, there were three scars on the palm of the left hand. The scars were adherent

to the underlying flexor tendons of the middle and ring fingers. A pedicle graft from the abdomen was used to cover the defect. Later, the sublimis tendon to the left middle finger was excised in the forearm and used as a graft for the flexor tendon to the middle finger. The palmaris longus tendon was grafted to the ring finger.

Ten weeks postoperatively, the patient had grasp and pinch mechanism in his left middle and ring fingers, and had resumed his regular work (Fig 4).



FIGURE 4 Postoperative Result in Case 3, Showing Range of Flexion in Middle and Ring Fingers after Tendon Grafting

CASE 4 A 21-year-old Negro received a laceration of the palm of his right hand when a jack handle broke. Three hours later the sublimis and profundus tendons to the right index finger were sutured in the palm. Eight weeks later,

the tendons and in the surrounding paratenon (Fig 6d) All scar tissue, including the matted sublimis and profundus tendons, was excised. A pedicle graft was cut from the abdomen. A split-thickness graft was cut from the thigh

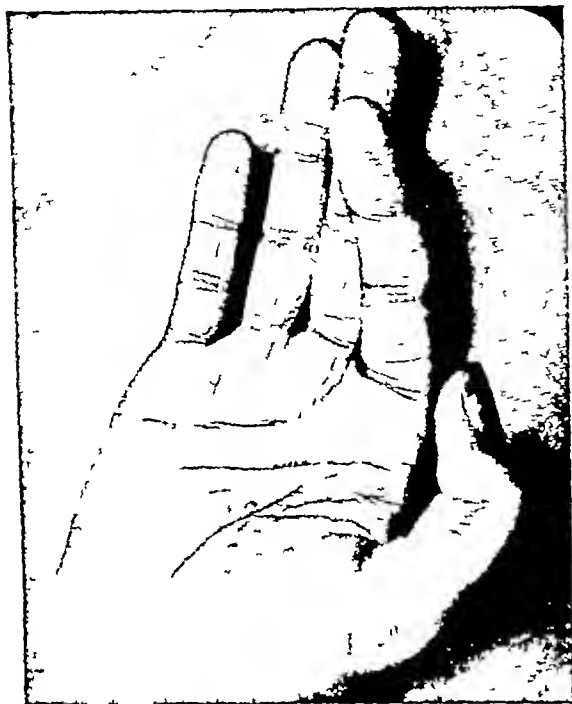


FIGURE 5 Loss of Flexion of the Right Index Finger Due to Separation at the Sutured Sites of the Tendons and Retraction of the Tendons, without Gross Infection (Case 4)

physical examination showed a 6-cm. scar over the radial longitudinal crease of the palm (Fig 5). In the right index finger, motions of the proximal joint were normal. Flexion at each interphalangeal joint, however, was entirely absent



FIGURE 7 Normal Range of Flexion, Ten Weeks after Operation, in Case 4

and sutured to the donor site on the abdominal wall. The free edge of the pedicle graft was then sutured to the defect on the palm of the right hand. Three weeks later the pedicle graft was detached from the abdomen and sutured to the palm of the hand. The defect on the abdomen was closed by suture of the skin edge to the split-thickness graft. The pedicle

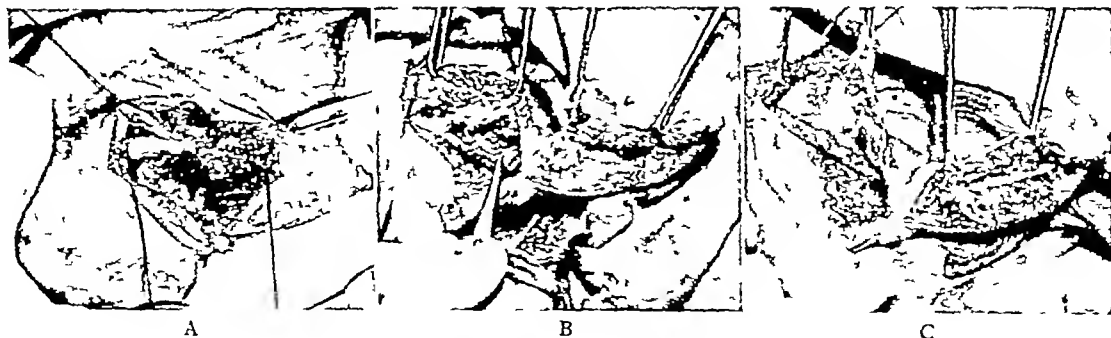


FIGURE 6 Operation in Case 4

A shows scoring between retracted tendons, B end of profundus and distal attachment of profundus tendon after excision (proximal annular ligament is preserved), and C suture of grafted tendon (scar in edge of graft may limit gliding of tendon)

actively but was possible 90° passively. Circulation and sensation of the right index finger were normal.

At operation the sublimis and profundus tendons were found separated at the previously sutured sites and retracted for about 1 cm. There was great scarring in the gap between

graft took well, and 3 weeks later an incision was made lateral to the pedicle graft. Through this the proximal end of the cut profundus tendon was exposed. A longitudinal incision was made over the middle of the lateral aspect of the right index finger from the base of the distal phalanx to the base

of the proximal phalanx. The sublimis and profundus tendons were excised from the index finger, 1 cm of profundus tendon being left at its attachment to the distal phalanx (Fig 6B). A longitudinal incision was then made in the forearm. The palmaris longus tendon was excised with a generous portion of paratenon on each side. The palmaris longus tendon was sutured to the proximal end of the profundus tendon with No 3 silk and Bunnell silk technic. The grafted tendon was then threaded beneath the carefully preserved proximal annular ligament into the finger. A small flap of bone was chiseled from the base of the distal phalanx. Two holes were drilled through the defect in the bone. A No 0 plain catgut suture was placed in the end of the tendon graft. The two strands of catgut were threaded through the two drill holes in the base of the distal phalanx. With traction on the sutures the distal end of the grafted tendon fitted snugly into the bone flap. The catgut sutures were then tied over a button on the dorsum of the distal phalanx. One silk mattress suture was placed, for reinforcement, in the remnant of the old profundus tendon and the end of the grafted tendon. It appeared that scar on one side of the pedicle graft might limit excursion of the grafted tendon (Fig 6C). Therefore, a block of paratenon was excised from the lower third of the lateral aspect of the thigh. A No 000 plain catgut suture was placed in each corner of the paratenon block. The paratenon was placed beneath the pedicle graft, the catgut sutures were carried through the palmar skin, and the lateral strands of the plain catgut sutures were tied in the palm. The wound was sutured with silk. The hand was immobilized in a plaster cast for 3 weeks. Silk sutures were removed in 1 week. After 3 weeks, the plain catgut sutures were wiped off the palm. Three weeks after operation the wounds were healed, and active motions were begun. Ten weeks postoperatively, there was essentially normal flexion in the index finger (Fig 7).

SUMMARY

Early recognition and early, proper treatment of acute suppurative tenosynovitis and trauma

will prevent the loss of function in the flexor tendons of the hand, but in more serious and improperly treated cases, the use of tendon grafts may restore useful function and obviate amputation.

Tendon grafting can restore function in a hand that has a loss of flexor action provided there is good circulation, normal joint function and normal sensation in the affected finger.

General considerations and operative principles for tendon grafting are presented.

Cases are reviewed in which tendon grafting restored pinch and grasp mechanism in hands with loss of flexor function after acute suppurative tenosynovitis and trauma.

A technic for tendon grafting for loss of flexor function in the hand is described.

I am indebted to Dr Thomas H Lanman for his criticisms and suggestions.

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THE EFFECTS OF BIS-TRIMETHYLAMMONIUM DECANE DIODIDE AND DIBROMIDE ON NEUROMUSCULAR FUNCTION AND ON INDUCED CONVULSIONS IN MAN*

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BALTIMORE

BIS-TRIMETHYLAMMONIUM decane diiodide (C_{10} diiodide) has been found to be a potent agent that blocks neuromuscular transmission in animals^{1,2} and in man.^{3,4} As predicted by Paton and Zaimis,² C_{10} has proved to be a useful substitute for d-tubocurarine in the production of skeletal-muscle relaxation for certain clinical purposes. This communication describes the results of the administration of C_{10} to normal subjects and prior to electrically induced convulsions.

C_{10} is a white crystalline substance easily prepared in pure form. It is freely soluble in water and can be sterilized by heat without any deterioration. It is miscible with procaine and Pentothal and does not produce any irritation when injected into tissues.

Paton and Zaimis² observed that small doses of this material produced in a variety of animals a

profound neuromuscular block. In certain species this appeared to affect the skeletal muscles to a greater degree than the muscles concerned in respiration. The neuromuscular block was not antagonized by neostigmine, but was counteracted by bis-trimethylammonium pentane diiodide. MacIntosh⁵ found C_{10} much less potent than d-tubocurarine in causing the liberation of histamine or heparin in animals, and in producing block at autonomic ganglions. C_{10} is apparently excreted largely in the urine.

RESULTS

Effect of Graded Doses on the Pattern and Degree of Neuromuscular Block

C_{10} , as either the diiodide or the dibromide salt, was administered intravenously in graded doses on 92 separate occasions to 5 normal subjects and to 13 psychotic patients. The ages of the subjects varied from nineteen to fifty-five years (average, forty years), and the body weights from 47 to 77 kg (average, 62 kg).

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After the administration of 1 mg of C_{10} dibromide over a period of five seconds to two minutes there was moderate limitation of the extraocular movements, but little or no effect on the muscle strength in the extremities or trunk.

When the dose was raised to 1.5 mg and injected over a similar period almost complete limitation of extraocular movements resulted. The patients could elevate the head and move the arms and legs but could not maintain this activity against even moderate resistance. The grip strength as measured by a hand dynamometer was reduced by approximately 50 per cent. There was no subjective respiratory distress, but occasionally there was mild dysphagia.

The intravenous administration of 2.5 to 3 mg of C_{10} diiodide or of 2 to 2.75 mg of C_{10} dibromide, over a period of five seconds to two minutes, produced complete or nearly complete relaxation of the muscles of the neck, arms, legs, shoulder girdle and pelvic girdle. Within forty-five seconds of the termination of the injection there was limitation of the extraocular movements with diplopia, followed within one or two minutes by complete paralysis of the extrinsic muscles of the eyes. At this period there was slight to moderate ptosis. During the two to four minutes after the administration of the C_{10} , during which transient fasciculations were occasionally seen, there was a progressive decrease in the strength of the muscles of the extremities and trunk until the patient was unable to move the head, arms or legs. Usually, the fingers could still be flexed, but the grip strength as measured by the dynamometer was always below 2 kg. At this stage there was only slight weakness of the facial, masticatory, lingual and laryngeal muscles, and slight to moderate weakness of the pharyngeal muscles. The subjects were able to shut the eyelids tightly, wrinkle the forehead, smile and purse the lips. Mastication was unimpaired, and the tongue could be protruded with ease. The voice was usually diminished in intensity, but only slightly slurred or nasal in quality. Swallowing was almost always subjectively difficult, but could be performed with some effort. There was little accumulation of saliva in the pharynx, and no choking. In 10 of the 18 patients there was no subjective respiratory distress, and no alteration of the respiratory rate or of the thoracic excursion. Vital capacity, however, was usually reduced by as much as 25 per cent. Eight of the subjects experienced mild to moderate subjective respiratory distress, with acceleration of the respiratory rate, in 2, thoracic excursion was consistently diminished, and abdominal breathing shallow, cyanosis developed and rhythmic oxygen insufflation became necessary.

When the dose was raised to 2.8 to 4 mg thoracic respiration was uniformly diminished or even ceased. Diaphragmatic movements were lessened and ac-

celerated, and thoracic and diaphragmatic respiratory movements became dissociated. The patients complained of respiratory distress, cyanosis developed, and artificial respiration, by means of rhythmic oxygen insufflation from a breathing bag, became necessary for a period of three to five minutes. In addition to depressing respiration these doses augmented the weakness of the facial and pharyngeal muscles, provoking difficulty in swallowing saliva, and diminished the intensity of the voice, with slurring of speech.

These effects of C_{10} were reproducible in any given subject from day to day. The effective dose and the relative effects on the peripheral and respiratory muscles varied in different subjects, and these differences bore no close relation to body weight.

Duration of the Effects

The duration of the maximum degree of weakness varied with the dose of C_{10} . The weakness lasted one or two minutes after the administration of 1 to 1.5 mg, three to five minutes after 2.0 to 2.75 mg and approximately seven minutes after 2.8 to 4.0 mg. Subsequently, strength returned progressively and rapidly, becoming normal sixteen to twenty-five minutes after the largest doses. At this time repetition of the original dose produced the same pattern of weakness, with no signs of any cumulative action of the drug.

Rate of Administration

The optimal rate of intravenous administration of C_{10} was found to be 1 mg per minute. More rapid injection resulted in little if any increase in the degree of peripheral relaxation and sometimes led to an irregular distribution of the effects, as indicated by a difference in the degree of weakness in the opposite extremities and occasionally by an increase in the degree of subjective respiratory distress. With slower administration (over two or more minutes) there was a significant decrease in degree of the resultant muscle weakness.

Maintenance Dose

The degree of paralysis produced by the administration of 2.0 to 2.75 mg could be maintained at a uniform level by further injections of 0.5 mg every four or five minutes, or 1 mg every eight to ten minutes. Because of the individual variations in the response to the drug, not clearly related to differences in body weight, careful observation of the patient was necessary to prevent respiratory depression and to maintain the desired degree of muscular weakness.

Use with Convulsive Therapy

If electric-shock therapy was administered after C_{10} , at the height of the resulting paralysis, the severity of both the tonic and clonic phases of the

convulsion was lessened. The optimum time for the administration of the electric shock was three to five minutes after the injection of C_{10} . The convulsive movements were softened, and the arms and legs could be passively moved with ease at all stages. A dose of 1.5 to 1.75 mg of C_{10} dibromide injected intravenously over a period of one or two minutes usually produced a degree of muscular relaxation that reduced the severity of the convulsion by about 50 per cent. There was no evidence that the softening of the convulsions diminished their therapeutic effect in the psychotic patients observed.

Effects Other Than Those upon Neuromuscular Function

No prominent subjective or objective effects of C_{10} were observed except on neuromuscular function. Occasionally, there was transient giddiness immediately after the injection of the drug, possibly associated with paresis of the extraocular muscles. There was no alteration of the state of consciousness or awareness of the patient. No changes were recorded in pulse rate or blood pressure in either normotensive or hypertensive subjects, unless the respiratory exchange was depressed sufficiently to produce anoxia and retention of carbon dioxide. Electrocardiograms obtained in several patients before and after the administration of C_{10} showed no abnormalities. The serum concentration of sodium and potassium, measured in several patients at the height of the paralysis, were all within the normal range. As has been noted, transient muscular fasciculations, especially over the chest and abdomen, were often observed immediately after the administration of C_{10} and before any prominent degree of paralysis had developed. Cholinesterase determinations on blood samples drawn at this period showed no alteration in the activity of this enzyme in plasma or erythrocytes. The spontaneous movements were thought to be due to a direct stimulating effect of the C_{10} .

No signs suggesting the release of any histamine-like substance followed intravenous administration. As much as 3 mg of C_{10} diiodide was injected intrarterially, and, although there was complete paralysis of the local area for over an hour, no redness, swelling, wheal formation, rise of skin temperature or increase in the secretion of gastric acid was noted. This is in contrast to the effect of d-tubocurarine, which invariably provokes all the manifestations mentioned above after intra-arterial administration.⁶ The intracutaneous injection of 0.1 mg of C_{10} di-bromide produced a transient flare and slight wheal without pseudopod formation, in contrast to the marked flare, wheal and pseudopod formation resulting from the same amount of d-tubocurarine.

The absence of any alteration in skin temperature or in blood pressure in the supine or erect positions

after the administration of C_{10} suggests that this substance has no appreciable blocking action on autonomic ganglions.

COMPARISON BETWEEN C_{10} AND D-TUBOCURARINE

Each of the 13 patients who received C_{10} prior to electric-shock therapy and 1 of the normal subjects also received d-tubocurarine on one or more occasions. The dose was sufficient to produce a degree of weakness of the trunk and extremity muscles comparable to that produced by 2.0 to 2.7 mg of C_{10} dibromide. In most cases this required approximately 60 to 80 units of d-tubocurarine (9 to 12 mg of the pentahydrate) administered intravenously over a period of two minutes. All the patients had greater weakness of the facial muscles than that after the administration of C_{10} , 8 had more pronounced weakness of the muscles of mastication and a greater degree of ptosis, 10 had more difficulty in swallowing, resulting in accumulation of mucus in the pharynx, a similar number had greater reduction in the intensity of speech, which became more nasal and slurred, and 6 had more impairment of respiratory function and weakness of the tongue. Thus, compared on the basis of dosage producing similar degrees of relaxation of trunk and extremities, the effects of d-tubocurarine upon the muscles of the oropharynx in most patients and upon the muscles concerned in respiration in some patients were more pronounced than those of C_{10} . Complete or nearly complete peripheral relaxation could be obtained by means of d-tubocurarine without appreciable subjective respiratory distress or marked dysphagia in some cases, but the number was smaller than that with C_{10} . As with C_{10} , in many patients having no subjective respiratory distress, the vital capacity was, nevertheless, reduced by as much as 25 per cent.

The rapidity of development of the neuromuscular block following the administration of d-tubocurarine was similar to that after C_{10} , but the duration of the weakness following d-tubocurarine was considerably longer, the maximum paralysis lasting for approximately ten minutes, in contrast to only four minutes after C_{10} . The time required for complete return of strength was approximately forty minutes after d-tubocurarine, in contrast to about twenty minutes after C_{10} . The length of time following a full dose at which an equivalent amount could be given without the production of any cumulative effects was approximately ninety minutes after d-tubocurarine and only about twenty minutes after C_{10} .

This shorter action of C_{10} and its comparatively lesser effect on the pharyngeal and respiratory muscles make it a more satisfactory agent for the production of muscular relaxation prior to electric-shock therapy than d-tubocurarine. It also lessens the dangerous results of respiratory depression

inadvertently produced by either overdose of the drug or unusual sensitivity on the part of the patient. Finally, C₁₀ has the additional advantage that it is less active in causing the release of any histamine-like substance.

It should be emphasized that the effective dose of C₁₀ dibromide is about a fourth that of d-tubocurarine on the basis of weight and about a third on the basis of molarity. The effective dose of C₁₀ dibromide is slightly less than that of C₁₀ diiodide on the basis of weight but is the same on the molar basis, indicating that the bis-trimethylammonium decane ion is the active group.

TREATMENT OF C₁₀ OVERDOSAGE

Paton and Zaimis¹ have reported that bis-trimethylammonium pentane salts (C₅) antagonize the neuromuscular blocking action of C₁₀. The amount of C₅ that can safely be injected (10 to 35 mg intravenously) is limited because of its potent action in blocking autonomic ganglions. This results in pronounced postural hypotension, which may last for several hours, and occasionally, especially in hypertensive subjects, in a striking drop in blood pressure in the supine position.

In our experience the intravenous injection of 15 mg of C₅ diiodide at the height of the muscular weakness produced by 3 mg of C₁₀ diiodide did not result in a more rapid return of strength than occurred spontaneously. However, the production of a high local concentration of C₅ by the intra-arterial administration of 5 mg at such a time did result in a slightly more rapid return of strength in the injected extremity.

Neostigmine, which antagonizes the neuromuscular blocking action of d-tubocurarine,⁷ had no effect on the degree of muscular weakness produced by C₁₀ dibromide or on the rate of return of strength.

Before the administration of either C₁₀ or d-tubocurarine a rubber airway and an oxygen tank with mask and breathing bag with which rhythmic insufflation of oxygen can be carried out should be available in case respiratory depression should develop. When C₁₀ is administered additional precautions are not evidently necessary in view of the short action of the drug.

SUMMARY

bis-Trimethylammonium decane diiodide and dibromide (C₁₀), potent blocking agents of neuromuscular transmission, are useful in the production of muscular relaxation prior to electrically induced convulsions. The advantages of C₁₀ for this purpose are shorter duration of action and more rapid recovery of motor power, less pronounced effects on the pharyngeal, laryngeal, facial and in some cases respiratory muscles, and the absence of any histamine-like effects.

We are indebted to Drs John Whitehorn and Nicholas Balloch for permission to study cases undergoing electric shock therapy. We also wish to thank Dr W. D. M. Paton of the National Institute for Medical Research, London, for a supply of C₁₀ and C₅ diiodide, and Dr E. J. deBeer, of The Wellcome Research Laboratories, Tuckahoe, New York, for providing us with 'Sincunne' (C₁₀ dibromide) and C₅ dibromide for use in these studies.

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THE USE OF BIS-TRIMETHYLAMMONIUM DECANE DIBROMIDE IN ANESTHESIA*

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BALTIMORE

SINCE 1942 partial curarization of patients during anesthesia has become an established procedure.^{1,2} This method, which provides satisfactory abdominal relaxation for surgical procedures and yet subjects the patient to a minimal degree of anesthesia, has obvious desirable features, but certain potential disadvantages. It has been convincingly demonstrated^{3,5} that the natural alkaloid, d-tubocurarine, may, upon parenteral injection, cause the release of a histamine-like substance, with consequent depression of blood pressure, bronchospasm and other undesirable reactions. Although these reactions are encountered infrequently during routine anesthetic procedures, they are always a possible source of difficulty in the susceptible patient.

In the event of temporary paralysis of the respiratory mechanism the trained anesthesiologist can maintain adequate ventilation by rhythmic manual compression of the rebreathing bag, but this does not precisely duplicate the results of the normal respiratory effort. d-Tubocurarine, if administered carefully, will produce profound abdominal relaxation with only moderate paralysis of the intercostal muscles and no appreciable impairment of diaphragmatic action. Transient apnea may be encountered, however, since the additional increment of drug affecting the diaphragm is a small fraction of that required for relaxation.

When Paton and Zaimis⁶ announced that bis-trimethylammonium decane diiodide (C_{10}) produced profound relaxation of extremity musculature, with little impairment of respiration, it was hoped that this favorable differential might also hold true for the abdominal muscles. With this possibility in mind, experimental and clinical studies were undertaken, and this communication is a preliminary report of the results.

The absence of any undesirable side effects of C_{10} ⁶ was first confirmed by one of us (D.A.H.) in laboratory experiments on animals anesthetized with the various general agents commonly used in our operating rooms. C_{10} was then used during the course of anesthesia in 172 patients undergoing major surgical procedures. In the large majority of cases the purpose was to obtain abdominal relaxation, but it was also employed to suppress coughing aggravated by an endotracheal tube

during light anesthesia, to relieve laryngospasm and to facilitate endotracheal intubation. An attempt was also made to quiet the respiratory effort for intrathoracic surgery by the use of C_{10} .

The surgical procedures included 158 abdominal and 3 thoracic operations, 4 craniotomies, 6 laminectomies and 1 radical dissection of the neck. It was planned to include in this series all patients to whom curare would have been administered. Exception to this rule was made in thoracic procedures for reasons discussed below. The patients ranged in age from sixteen to seventy-eight years, the average age being forty-five years, no attempt was made to select patients according to their evaluation as surgical risks.

RESULTS

The most satisfactory method for administration of C_{10} proved to be the following: 1 to 2 mg of the dibromide salt in a solution containing 1 mg per cubic centimeter were injected intravenously at a rate not exceeding 1 mg per minute, through the same tubing used for administering Pentothal or an intravenous infusion. Doses of 0.5 to 1 mg were then injected at intervals of five to ten minutes for as long as "curarization" was desired. When a period of twenty minutes or longer had elapsed since the previous dose, the initial dose could be repeated. Doses in excess of 1.5 to 2.0 mg were found likely to cause respiratory depression. The margin between the dose of C_{10} that produced adequate abdominal relaxation and that which produced some respiratory depression was usually small, and in a number of cases the amounts were identical. Injection rates more rapid than that recommended were prone to cause respiratory depression or transient apnea even when the amount injected did not exceed 1 mg.

The maximum total dose was 10 mg administered in six injections of 1 or 2 mg each over a seventy-minute period. Relaxation during this operation, a lumbar sympathectomy, was not deemed satisfactory, implying that insufficient dosage was employed. The largest single dose given was 2.5 mg (over a two-and-one-half-minute period), although 4 mg injected over a five-minute period was well tolerated.

Satisfactory abdominal relaxation followed the administration of C_{10} during 130 abdominal operations. The general anesthetic employed was Pentothal and nitrous oxide in 105 cases, ether (alone or in combination with other agents) in 18, and ethylene, cyclopropane or spinal anesthesia, supplemented by one or more of the agents men-

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tioned above, in the remainder. In all cases the depth of anesthesia was maintained in the upper planes of the third stage. During 18 other abdominal operations only fair relaxation was obtained with C_{10} , and in 10 others relaxation was unsatisfactory. It is believed that failure to obtain satisfactory relaxation was due to the administration of insufficient amounts of C_{10} , rather than to variations in the response of some patients to the drug. The duration of action of C_{10} is short, and unless frequent small doses are given "decurationization" occurs.

C_{10} fully controlled the cough reflex in 6 cases, it failed to do so in 1 patient in whom coughing was subsequently adequately controlled with d-tubocurarine. The drug satisfactorily facilitated endotracheal intubation under Pentothal anesthesia, and relieved laryngospasm encountered during a stormy ether induction. It did not appear to lessen the amount of Pentothal required to maintain an adequate plane of anesthesia.

Observable respiratory depression was encountered in 94 patients or 55 per cent of the series. This was usually manifested by a decrease in tidal volume and minute volume, with no change or an increase in the respiratory rate. These alterations were usually accomplished by activation of the anterior strap muscles of the neck. The type of respiratory depression produced by C_{10} seemed to differ somewhat from that produced by d-tubocurarine, which caused a quieter respiratory effort similar to that resulting from deep etherization. C_{10} , although weakening the respiratory effort, caused jerking, spasm-like contractions of the diaphragm that were annoying to the surgeon, especially during intrathoracic operations or those on the upper abdomen. Hiccups occurred during the operative period in 9 patients. The more severe depressions rarely persisted for more than six or seven minutes. Total apnea was not encountered.

The blood pressure and pulse rate did not fluctuate significantly in 148 cases after the administration of C_{10} . In 18 patients, in whom incompletely compensated respiratory depression was permitted to occur, broad alterations in cardiovascular activity did result, presumably secondary to partial asphyxia. One patient experienced a two-to-one heart block five minutes after receiving 25 mg of C_{10} . This persisted for approximately twenty minutes, during most of which there was appreciable respiratory depression. This arrhythmia reverted spontaneously and did not recur after subsequent injections of C_{10} .

Pentothal and nitrous oxide were the principal agents employed in 129 procedures, ether in 27 cases, ethylene, with or without ether, in 8, and cyclopropane, once alone and twice with Pentothal. In 5 cases spinal anesthesia was supplemented with Pentothal, nitrous oxide and C_{10} , or with ethylene and C_{10} . No obvious potentiation of the effect of C_{10} by any of these agents was observed. Dosage

and response to C_{10} were essentially similar regardless of the general anesthetic used.

No deaths occurred either in the operating room or during the immediate postoperative period. In general, the postoperative course of the patients seemed unusually benign, without adverse respiratory or cardiovascular manifestations. This is believed to be due, at least in part, to the lighter planes of anesthesia that were employed in the presence of adequate "curarization." Postoperative atelectasis or pneumonia was not observed. In 1 patient, a sixty-one-year-old woman who underwent a gastric resection for benign duodenal ulcer, moist basal rales were heard during the first twenty-four hours after operation and cleared spontaneously. Four patients died five or more days after operation. In no case was the cause of death in any way related to the anesthetic agents or technique.

DISCUSSION

The limited experience with C_{10} in anesthesia does not permit any final evaluation of its usefulness. The brief duration of its action necessitates more frequent injections than those required with d-tubocurarine. This imposes a burden on the anesthetist, as does the increased incidence of respiratory depression that results. On the other hand a standard dosage range may be used regardless of the anesthetic agent employed, since no potentiating effect is evident, as when d-tubocurarine is administered to patients under ether anesthesia. In the present studies there have been no effects of C_{10} that might be attributed to the release of any histamine-like substance.

SUMMARY

bis-Trimethylammonium decane dibromide (C_{10}) was employed as a "curarizing" agent during 172 general anesthetics. It was found to be capable of providing adequate abdominal relaxation, but was not without some interference with respiration. Its effect was of considerably briefer duration than that of d-tubocurarine. Its action was not potentiated by ether.

We are indebted to Dr. Alfred Blalock, Miss Olive Berger, R.N. and the Anesthesia Staff of the Johns Hopkins Hospital, whose co-operation made this study possible.

The bis-trimethylammonium decane dibromide (Syncurine) used in this investigation was generously provided by Dr. D. S. Searle, medical director, and Dr. E. J. deBeer, director of research, Burroughs Wellcome and Company, Tuckahoe, New York.

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MEDICAL PROGRESS

MEDIASTINAL EMPHYSEMA*

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MEDIASTINAL emphysema, its precursors and its sequelae have been known to clinicians for well over a century. Laënnec,¹ in his treatise on diseases of the chest, published in 1819, gave an amazingly accurate description of the condition under the heading of "interlobular emphysema." He was thoroughly familiar with certain phases of its pathogenesis, many of its symptoms and signs and its treatment. Similarly, Muller,² in 1888, advanced concepts concerning mediastinal emphysema, closely paralleling those of today. One of the characteristic physical signs — namely, the presence of bubbling crepitations occurring synchronously with the heart beats, and now usually referred to as Hamman's sign — was not unknown to Muller. Considerable case material was added to the literature after the influenza pandemic of 1918, and extremely detailed and accurate clinical descriptions of the development, course and sequelae of mediastinal emphysema are to be found in these writings.^{3, 4} In 1934 Hamman⁵ reported 3 cases of interstitial emphysema of the lungs, and a few years later he employed the term "spontaneous mediastinal emphysema."^{6, 7} In the many articles on this subject that followed, the use of the term "spontaneous" became widespread. Many of these subsequent reports presented cases in which factors of importance regarding the pathogenesis of mediastinal emphysema were obviously operative. Yet they were referred to as cases of spontaneous interstitial or mediastinal emphysema. The occurrence of this condition in the newborn, in asthma and during labor may be cited as examples. It is not unlikely that in all cases certain predisposing and precipitating factors exist, although in some cases these may be overlooked or may escape detection. In many patients the development of mediastinal emphysema proceeds slowly, so that the diagnosis is not made until several days have elapsed. Under such circumstances predisposing factors such as strenuous exercise and acts of straining are relegated to the background, and are not mentioned by the patient or inquired about by the physician. It appears, then, that the use of the word "spontaneous" serves no gainful purpose. On the other hand, it may deter the physician from critically

analyzing accompanying circumstances or from carefully evaluating some of the patient's activities during the few days preceding the onset of symptoms.

Laënnec, as early as 1819, was well aware of certain predisposing factors, and stated that "the most common of these is the prolonged forcible retention of the breath during powerful and long continued exertions, as in child-bed, in relieving the bowels when constipated, and particularly in raising heavy weights." He also commented that children were more subject to the disease than adults. "In them it occurs frequently during an attack of croup, or in severe catarrhs in which the bronchial obstruction is very great."¹ The accuracy of these statements is pointed out below.

The term "mediastinal emphysema" should be thought of as representing only one link in a chain of events. Its important precursor, pulmonary interstitial emphysema, and its many sequelae, such as subcutaneous emphysema, pneumothorax and pneumoperitoneum, should always be kept in mind.

Mediastinal emphysema has almost invariably been regarded as benign. However, one should not lose sight of the fact that it not infrequently endangers life. This has been stressed by the Macklins,⁸ who have employed the word "malignant" in describing these cases. The importance of the recognition of evidences of circulatory and respiratory embarrassment should be emphasized, since surgical intervention in some cases may be life saving. This is clearly brought out in Case 5 presented below and in a recent report by Karns and Daue.⁹ In each case a fatal outcome was averted by the performance of a mediastinotomy. Again, a similar procedure was not unknown to Laënnec, for he stated that "when the aerial infiltration extends to the external parts, a few pricks with the lancet at the lower part of the neck usually suffice to dissipate it."¹

SEQUENCE OF EVENTS IN THE DEVELOPMENT OF MEDIASTINAL EMPHYSEMA AND ITS SEQUELAE

A great contribution to the understanding of the pathogenesis of mediastinal emphysema has been the experimental work and clinical correlation of the Macklins.^{8, 10, 11} The primary event is rupture of the walls of the alveoli. Only alveoli whose bases rest against bronchi, bronchioles,

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blood vessels, connective-tissue septums and pleura—the so-called “marginal” or “nonpartitional” alveoli—are concerned in the process “Partitional” alveoli whose bases lie against adjoining alveoli are not involved. As a result of rupture of the “marginal” alveoli air gains access to the underlying connective tissue. The transport of air thence occurs by way of the sheaths of the pulmonary blood vessels, the sheaths of the bronchi and bronchial blood vessels playing no role in this regard. By continued dissection along the pulmonary blood vessels, interstitial pulmonary emphysema supervenes, to be followed, with further dissection, by mediastinal emphysema. In some cases air may proceed subpleurally, resulting in the formation of subpleural blebs. The mediastinum may again be reached as the air progresses beneath the pleura. With the development of mediastinal pressures above that of atmosphere rupture may take place, resulting in pneumothorax. An alternative mechanism for the formation of pneumothorax is rupture of one of the subpleural blebs. The pneumothorax in most cases is on the left side. The trapped air may seek other escape channels: the subcutaneous tissues of the head, neck, chest, abdomen, back and extremities, the retroperitoneal tissues, and the peritoneal cavity. The progress of air along these channels is aided by the movements of respiration and by the building up of pressures within the tissues, which enhance routes of escape.

FACTORS INVOLVED IN RUPTURE OF THE “MARGINAL” ALVEOLI

A considerable amount of information about the mechanisms of alveolar rupture is attributable to the work of the Macklins, cited above, in which details are given. All have a single common factor—namely, a pressure gradient between alveoli and adjoining vessel sheath. Factor A of Macklin operates in cases in which the alveoli are over-expanded through overinflation of the lungs, without a concomitant widening of the lumen of the blood vessels upon which they border, thereby permitting the creation of a pressure gradient between the two, and allowing rupture. Factor B of Macklin exists when there is a reduction in the caliber of the pulmonary blood vessels without a corresponding diminution in the size of the alveoli, a similar pressure gradient being established. In certain cases a combination of these factors co-exists. However, leakage of air may fail to take place, in spite of overinflation of the lungs, if a simultaneous increase in the caliber of the blood vessels occurs. Thus, in massive collapse of the lung, the affected side receives less blood, whereas the hyperinflated uninvolved lung receives a correspondingly greater amount of blood. Alveolar rupture, as a result, does not occur. Similarly, after pneumonectomy the remaining lung that undergoes hyperinflation receives a greater volume

of blood, and the relation of alveoli to vessel sheaths remains intact.

A review of clinical cases of mediastinal emphysema demonstrates certain predisposing and precipitating factors of importance. The most significant of these is the production of local overinflation of the lung, which may result from a variety of causes. The following list is offered as a working clinical classification of the conditions under which mediastinal emphysema may be encountered.

Atelectasis with associated alveolar ectasia (compensatory hyperinflation of adjacent alveoli)

Infectious diseases (upper-respiratory-tract infections, pneumonia, tuberculosis, measles, influenza, pertussis, diphtheria, smallpox and so forth)

Inhalation of foreign bodies

Neoplasms of the lung

Atelectasis of the newborn (following the inhalation of meconium, mucus, secretions and so forth before or after birth)

Bronchial asthma

Increased intra-alveolar pressure resulting from forceful respiratory efforts against resistance

Closure of glottis (parturition, coughing, violent exercise, acts of straining)

Laryngospasm (pertussis)

Acute obstructive laryngitis (diphtheria, streptococcal infections)

Bronchial asthma

Playing of wind instruments, glass blowing and so forth

Tracheal insufflation

Intratracheal anesthesia

Resuscitation of the newborn, drownings, electrocutions and so forth by such methods as intratracheal insufflation and use of the pulmotor

Positive-pressure inhalation therapy

Combinations of these factors

It is obvious that patients are frequently seen in whom one or more factors predisposing to the development of mediastinal emphysema exist and yet rupture of alveoli does not occur. For example, one may observe cases of status asthmaticus complicated by atelectasis and patchy bronchopneumonia in which none of the symptoms or signs of mediastinal emphysema are found, although the physician has constantly been on the alert for them. Why one patient falls victim to this condition, whereas another, duplicating all existing circumstances, does not, remains unexplained, and this has raised the inevitable factor of constitutional predisposition.

SYMPTOMATOLOGY

The nature and severity of the symptoms depend in general on the degree of distention of the lung

MEDICAL PROGRESS

MEDIASTINAL EMPHYSEMA*

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Brief comment regarding the mode of production of tension pneumothorax is warranted, in view of the widespread impression that air becomes trapped in the pleural cavity by some valvular mechanism during the phase of inspiration. The only time that air can enter the pleural cavity against the high tension of the latter is when the pressure of the air in the affected lung is higher than that in the pleural space. This situation is encountered during such acts as coughing or straining, when the glottis is momentarily closed, as a result of which high pressures are built up within the lung. Air will thus be added to the pneumothorax only during acts of forceful expiration. This fact has frequently been confirmed by measurements of intrapulmonary and intrapleural pressures in human cases.¹⁹⁻²¹

The detection of subcutaneous emphysema needs little comment. It is a sign that is commonly overlooked. Its presence should make one suspicious immediately of the diagnosis of mediastinal emphysema. Its significance was appreciated by Laënnec, who commented that "should an external emphysema make its appearance at the same time, beginning in the neck, the diagnosis of course is rendered more certain." This finding most commonly involves the neck, the supraclavicular and infraclavicular fossae and the axillae. In some cases subcutaneous crepitation may be elicited over the back, abdomen, extremities and genitalia. An example of extensive generalized subcutaneous emphysema involving the head, neck, chest, abdomen, back, lower extremities and genitalia is presented in Case 6, described below.

In uncomplicated cases the temperature is usually normal. Occasionally, low-grade elevations are seen.

The blood pressure generally remains within normal limits, although not infrequently one observes an initial rise. In cases in which marked increases in mediastinal pressure are encountered, so that a tamponade effect exists identical to that seen in massive pericardial effusion, the blood pressure may fall. This has frequently been noted clinically, and has been reproduced experimentally. In such cases measures to overcome the increased mediastinal tension must be employed.

ELECTROCARDIOGRAPHIC CHANGES

In the majority of cases electrocardiographic changes are absent. Approximately 25 per cent of records show positive findings, but no characteristic pattern is presented. The significant abnormalities have been changes in the T waves, deviation of the ST segments from the isoelectric line, absent or greatly reduced initial deflection in the standard Lead I, decreased voltage and shifts in the electrical axis.^{7, 18, 22, 23} Pneumothorax per

se may produce similar changes.^{24, 25} Inversion of the T waves in all the conventional leads has been observed. In a recent report marked elevation of all the ST segments was noted.²⁶ In another case discussed by the same author the voltage of the QRS complex was trebled when the patient assumed the upright position. Significant alteration of voltage with change of position did not follow recovery. A third case presented a wandering auricular pacemaker, with resumption of normal sinus rhythm within five days. The electrocardiographic changes are generally transient, reversion to normal taking place in seven to fourteen days.

X-RAY FINDINGS

There seems to be little doubt that the diagnosis of mediastinal emphysema is often not suspected, and x-ray examination of the chest not made. On the other hand, the diagnosis, when suspected on clinical grounds, has not infrequently been ruled out on the basis of a single film taken in the postero-anterior projection. It should be emphasized that serial studies may be necessary, and that lateral views of the chest are essential, to demonstrate air trapped behind or in front of the heart. Air in the mediastinum is often visible as streaks of increased radiance running along the borders of the heart. The presence of air streaks along fascial planes and air pockets in subcutaneous tissue may be readily detected. Further aid, radiographically, may be furnished by the demonstration of pneumoretroperitoneum and pneumoperitoneum. As mentioned previously, x-ray examination is invaluable in disclosing a small pneumothorax not manifest clinically.

DIFFERENTIAL DIAGNOSIS

The chief difficulty in differential diagnosis arises from the similarity of the pain of mediastinal emphysema to that of primary cardiac disease, and from the presence in some cases of dyspnea, cyanosis, distention of veins and electrocardiographic changes.^{5, 22, 26, 27} The major illnesses that enter into consideration are angina pectoris, myocardial infarction, dissecting aneurysm of the aorta, pericarditis, mediastinitis and pulmonary embolism.

TREATMENT

Only symptomatic treatment is required in most cases. Because of the possibility of recurrences, bed rest should be insisted upon, even when symptoms are minimal. In the presence of markedly elevated mediastinal pressure, associated with increasing dyspnea, cyanosis and changes in blood pressure, incision above the suprasternal notch, to create a channel for the escape of air, may be life saving. In patients with tension pneumothorax decompression of the pleural space is indicated.

and mediastinum, the accessibility of escape channels and the anatomic location of the escape channels. The two important systems of the body involved are the respiratory and the circulatory. Respiration may be seriously interfered with by the splinting action of the air in the connective tissue of the lung. The lung, as a consequence of interstitial emphysema, may become extremely voluminous and rigid. The result is dyspnea, the degree of which will depend on the extent of the underlying process. Macklin refers to this as "airlock." Circulation may be hampered by means of the collapse of the pulmonary vessels, causing venous stasis and cyanosis—the "air-block" of Macklin. With increasing mediastinal pressure the function of the great veins entering the heart is impeded by compression, and the venous return not only from the lungs but also from the systemic circuit is thus impaired. Direct effect upon cardiac function is brought about by such factors as decreased venous return, tamponade identical to that seen in massive pericardial effusion and impairment of coronary blood flow.

The development of escape channels may have a markedly beneficial effect symptomatically. Subcutaneous emphysema, for example, acts to decompress the mediastinum, and dramatic amelioration of dyspnea and cyanosis may be observed under such circumstances. A reciprocal relation between mediastinal pressure and subcutaneous emphysema has been noted experimentally.¹⁴ The development of pneumothorax may similarly release increased mediastinal pressure. However, in patients in whom tension pneumothorax supervenes, augmentation of dyspnea and cyanosis occur.

The most frequently encountered symptom of mediastinal emphysema is chest pain, which, because of its various characteristics, has often been mistaken for angina pectoris or myocardial infarction. The onset of pain is sudden in most cases, although not invariably so. Its location is inconsistent, the commonest sites being precordial, substernal, the anterior portion of the chest, axillary, the posterior portion of the chest and midscapular. Radiation to the neck, left shoulder, left arm or back may occur. The intensity of the pain varies from case to case, being a mild form of discomfort in some and actually agonizing in others. It has been referred to as sharp, stabbing, knife-like or squeezing. It may be intensified in left lateral recumbency, and alleviated when the patient assumes the upright position. Just as in dyspnea and cyanosis, the establishment of escape channels may produce relief of pain. The duration of this symptom varies from momentary discomfort to pain lasting hours or days. Its disappearance is generally gradual.

In certain cases patients have been aware of the sensation of air within the chest, and some

have been able to hear it. Laënnec stated that "patients are sometimes sensible of a kind of crackling in the part affected."

Various other symptoms have been associated with mediastinal emphysema, among them anxiety, sweating, palpitation, epistaxis, dysphagia and pain on motion of the neck. When air has dissected retroperitoneally and into the subcutaneous tissues of the back, the patient may complain of back pain. Similarly, the presence of pneumoperitoneum may be associated with abdominal pain, and on occasions a surgical condition of the abdomen has been simulated.

PHYSICAL SIGNS

There are four signs of diagnostic importance in mediastinal emphysema. These are mediastinal crepitation, decrease or obliteration of cardiac dullness, subcutaneous emphysema and pneumothorax.

The presence of air in and about the mediastinal tissues produces sounds that have been variously described as crackling, clicking, bubbling, crunching, grinding, rasping, snapping, simulating the rattle of dried peas on a taut canvas, the crinkling of cellophane, the sounds of footsteps in packed snow on a dry, brisk day, the squeaking of a leather saddle, the cooing of doves and the rubbing together of distended balloons.¹⁵ Laënnec refers to this as "the dry crepitous rhonchus with large bubbles." Apart from these purely subjective characterizations, the sound produced by the bubbles of air has certain objective features. It is generally most easily detected in the left lateral recumbent position and during the expiratory phase of respiration. It is less readily audible when the patient is upright. The sound accompanies both systole and diastole, but may be louder during systole. Its relation to the cardiac cycle has been demonstrated phonocardiographically.^{15 16} The presence and the intensity of the sound are variable. When faint it may be mistaken for a pericardial friction rub. The duration of this finding varies from hours to several weeks, the average being about one week.

Diminished cardiac dullness, or hyperresonance over the sternum and precordium, is best elicited with the patient recumbent. In the upright position, and particularly when the patient leans forward, this sign may disappear. In many cases the maneuver of alternate percussion in the recumbent and forward positions may be of decided help diagnostically.

Of interest regarding the presence of pneumothorax is the fact that it is most often on the left side. Few instances of right-sided pneumothorax have been recorded.^{17 18} No adequate explanation for this has ever been offered. It should be borne in mind that in many cases the pneumothorax may be very small and may escape detection on physical examination. Conversely, one should study care-

fully all cases of so-called spontaneous pneumothorax, particularly those on the left side, for evidences of mediastinal emphysema

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Throughout this discussion consideration of mediastinal emphysema secondary to fractured ribs, blast injuries, other forms of trauma to the chest, caisson disease, rupture of the esophagus and so forth has deliberately been omitted. In such cases, factors other than those stressed here may be operative, some of which, on the basis of present knowledge, are not entirely clear.

CASE REPORTS

CASE 1 D C, an 18-year-old college student and athlete was admitted to the Boston City Hospital on July 11, 1940, complaining of pain in the chest of 1/2 hour's duration. He had been well until 1 week prior to admission, when a "cold" characterized by nasal congestion and cough productive of whitish sputum developed. Half an hour before entry to the hospital, while walking along the street, he suddenly experienced a sharp, stabbing, knife-like pain over the precordium, radiating to the left upper quadrant of the abdomen, the left shoulder and down the inner aspect of the left arm as far as the elbow. The pain became progressively more severe, was accentuated by respiration, was not relieved by rest and was associated with what the patient termed "a scraping noise in the chest."

Physical examination revealed diminished tactile and vocal fremitus over the upper half of the left side of the chest, posteriorly, and distant heart sounds.

The temperature was 99°F, the pulse 84, and the respirations 22. The blood pressure was 130/92.

On the following day a house officer reported the presence of a "variable friction rub" heard best just to the right of the xiphoid, accentuated on inspiration and absent in the sitting position. The white-cell count and sedimentation rate and an electrocardiogram were within normal limits. X-ray examination of the chest was reported as negative. On the 6th hospital day mediastinal crepitation was still audible at the lower end of the sternum. The patient was discharged on this day, against advice.

Two days after discharge from the hospital he was readmitted because of recurrence of chest pain similar to that experienced initially. Examination at this time revealed increased resonance over the left side of the chest, anteriorly and posteriorly, associated with decreased tactile fremitus and breath sounds. Mediastinal crepitation was readily audible to the left of the sternum, and extended to the fifth intercostal space. The blood pressure was 100/70. A repeat electrocardiogram and roentgenogram of the chest were normal. On the 5th hospital day mediastinal crepitation was no longer heard. The patient was discharged on the 10th day, asymptomatic, and showing no abnormalities physically.

CASE 2 A 15-year-old schoolboy was admitted to the Boston City Hospital on August 12, 1940, because of a paroxysm of bronchial asthma. He had been subject to asthmatic attacks since the age of five years, usually more severe during the summer months, when he also suffered from hay fever. The present paroxysm had begun on the evening prior to the day of admission.

Physical examination revealed moderate respiratory difficulty, congested nasal passages, diffuse rhonchi throughout both sides of the chest and slight cyanosis of the nail beds and lips.

The blood pressure was 125/100, the temperature 99.8°F, the pulse 99, and the respirations 24.

On the following day subcutaneous emphysema involving the anterior aspect of the neck and both supraclavicular fossae was detected physically, and a crackling sound synchronous with the heart beat was heard along the left border of the sternum. An x-ray film of the chest revealed air in the subcutaneous tissues, but no air was demonstrated in the mediastinum. Only the posteroanterior projection was taken. The above findings gradually disappeared, and the patient was discharged on the 10th hospital day.

CASE 3 N T, a 17-year-old schoolgirl, was admitted to the Boston City Hospital on September 21, 1942, because of severe frontal headache and pain over the anterior aspect

of the chest and neck of 24 hours' duration. She was known to have had asthma since early childhood. On the evening before admission she had been awakened from sleep by a paroxysm of difficulty in breathing, which had become progressively severe to the time of entry. Six hours later the dyspnea had become intense and was associated with cyanosis. It was noted that the patient's neck had become swollen, and she complained at this time of moderately severe substernal and precordial pain, radiating to the left shoulder.

On physical examination the patient was found to be dyspneic and slightly cyanosed. She complained of pain on motion of the neck. Subcutaneous crepitation was elicited on the right side of the neck and over the suprasternal notch. These areas were tender on pressure. Coarse rhonchi were audible throughout both lungs. Breath sounds, tactile fremitus and vocal fremitus were diminished anteriorly over the left upper lobe. A "crepitant sound synchronous with the heart beat" was heard in the region of the apex. This sound was reported as being of variable intensity and inconstant.

The temperature was 98.6°F, the pulse 90, and the respirations 24.

X-ray study of the chest showed moderate bilateral emphysema and a small pneumothorax involving the left upper lobe.

On symptomatic treatment the findings described above rapidly returned to normal, and the patient was discharged feeling well on the 8th hospital day.

CASE 4 C C, an 18-year-old girl who had had paroxysms of bronchial asthma since childhood, was admitted to the Boston City Hospital on November 13, 1946. Her present illness had begun at 4 a.m. on the day of admission, when she was suddenly awakened by a "tight feeling" beneath the sternum, associated with respiratory distress and wheezing. Shortly after the onset of these symptoms she experienced a "sharp, tearing pain," substernal in location, with radiation upward to the neck. This was accompanied by a sensation of choking. Self-administration of epinephrine and intravenous injection of aminophylline given later by her personal physician afforded no relief. Dyspnea became progressively worse, and she was hospitalized.

On entry the patient was in moderate respiratory distress. Subcutaneous crepitation was felt over the neck anteriorly, in both supraclavicular fossae and in the left infraclavicular fossa. The right side of the chest was more resonant than the left, approaching hyperresonance posteriorly. Expiratory wheezes were audible throughout both lung areas. There were impaired resonance and diminished breath sounds at the left base posteriorly. Mediastinal crepitation was not heard.

The temperature was 101°F, the pulse 104, and the respirations 24. The blood pressure was 110/70.

X-ray examination of the chest on the day after admission showed displacement of the heart and trachea to the left, elevation of the left leaf of the diaphragm, diffuse density involving the lower half of the left-lung field, extensive subcutaneous emphysema of the neck and shoulders and the presence of air along the left border of the heart.

The patient was treated with sedatives, ephedrine sulfate, intravenous injection of aminophylline and intramuscular administration of penicillin. Symptoms gradually subsided, and the temperature remained normal from the 6th day on. On the 10th hospital day x-ray examination of the chest was reported as within normal limits. The patient was discharged completely asymptomatic on the 14th day.

CASE 5 I B, a 19-year-old girl, was admitted to the Boston City Hospital on March 26, 1943, because of severe substernal pain, cough and dyspnea of 8 hours' duration. Three days before entry coryza characterized by nasal congestion and discharge developed. On the day prior to admission she engaged in sports, and that evening she danced for several hours. She retired at an early hour, and, except for a "head cold" and fatigue, felt fairly well. Fifteen minutes after being in bed she became nauseated, and vomited several times. This was soon followed by a paroxysm of coughing, during which she experienced severe, knife-like pain beneath the xiphoid, radiating through to the back. At the same time she became markedly dyspneic and orthopneic. The pain

*Previously reported by VanderLaan and Marsh.¹

grew progressively worse, and was intensified by inspiration and coughing.

Physical examination revealed marked respiratory distress. There was extensive subcutaneous emphysema involving the neck, face, occiput, supraclavicular and infraclavicular fossae, both breasts and the upper portion of the back. The precordium was hyperresonant to percussion, and the cardiac borders were not made out. Breath sounds were diminished bilaterally. The heart sounds were distant. Mediastinal crepitation was not elicited. The epigastrium was tender on pressure.

The temperature was 100.2°F, the pulse 108, and the respirations 30. The blood pressure was 130/95.

X-ray study of the chest at the time of admission showed only extensive subcutaneous emphysema. An electrocardiogram taken 2 days after entry was interpreted as within normal limits.

On the 2nd hospital day "muffled crackling sounds" synchronous with the heart beat were audible along the left sternal border, but these disappeared on the same day. With symptomatic therapy, including the use of oxygen, there was steady improvement in her condition.

On the 4th hospital day the patient suddenly took a turn for the worse. Severe dyspnea and cyanosis rapidly developed, and pain beneath the xiphoid was intense, 0.03 gm (1/2 gr) of codeine sulfate, 0.2 gm (3 gr) of phenobarbital, and 100 mg (1/6 gr) of morphine sulfate, given within a period of 1/2 hour, failed to relieve the pain. Oxygen administered by Boothby mask was without effect. The respirations rose to 40, and the pulse to 140. The blood pressure was 160/120. Subcutaneous emphysema recurred, was more extensive than previously and involved the face, head, neck and chest. The respirations continued to rise, and were shallow.

X-ray examination of the chest, done at the bedside, demonstrated the presence of air along the left border of the heart. An electrocardiogram at this time revealed diphasic T waves in Lead 2 and 3, with depression of the ST segments.

Because of the marked respiratory embarrassment, a thoracic surgeon was consulted, and the patient was transferred to the operating room, where a low-collar thyroid incision was performed under local anesthesia. This resulted in a dramatic and almost instantaneous relief of symptoms. When the patient was returned to the ward she was breathing normally, her color was markedly improved and her chest pain had gone. Her convalescence from then on was uneventful, and she was discharged well on the 13th hospital day.

CASE 6 W. S., a 78-year-old man, was admitted to the Boston City Hospital on May 22, 1947. For the past 30 years he had had repeated episodes of cough, expectoration and dyspnea, particularly during the winter months. He had worked as a laborer up until 20 years previously, when he had been forced to give up his job because of shortness of breath. During the 4 months prior to admission there had been a marked increase in the severity of dyspnea on exertion, and the cough had become more persistent. Because of the progression of these symptoms, he was referred to the hospital by his physician.

On entry the patient was dyspneic and the rate of respiration was 40 per minute. Expansion of the chest was limited but equal. There was hyperresonance to percussion bilaterally. The breath sounds were diminished, and rhonchi were audible throughout both lungs. Moist rales were heard at the right base. No cardiac enlargement was made out. The heart sounds were distant and regular. The blood pressure was 140/80. The fingers were clubbed.

X-ray examination of the chest on the day after admission showed a partial pneumothorax at the left base, with an estimated 30 per cent collapse of the left lower lobe. Five days later the lung fields were reported as being emphysematous; no evidence of the previous pneumothorax having been demonstrated.

During this interval treatment had consisted of supportive measures, intramuscular administration of penicillin and oxygen. The patient had shown definite improvement in the dyspnea and cough.

On the 10th hospital day he suddenly became markedly dyspneic, and physical examination disclosed evidence of a tension pneumothorax on the left. Thoracentesis was immediately performed and 1000 cc of air was removed from the left pleural cavity. The needle was fixed to the chest

wall, and connected to a rubber tube the other end of which was immersed in water. On the following day, because of mechanical difficulties with the apparatus, the needle was replaced by an intercostal catheter inserted into the seventh interspace. During these 2 days progressive and extensive subcutaneous emphysema was observed, involving the neck, face, chest, abdominal wall, thighs, legs and genitalia. Considerable air was removed by means of mechanical suction through a 16-gauge needle placed in the subcutaneous tissue of the left anterior side of the chest. In spite of these attempts at decompression, the patient died on the 13th hospital day, 4 days after the onset of the tension pneumothorax.

At autopsy, performed 7 hours after death, there was extensive subcutaneous emphysema of the entire body. The serotum was distended by air, which could be forced into the lower abdominal wall by compression. Numerous blebs of varying size were present in the retroperitoneal tissues, especially about the descending colon. The left pleural cavity contained air and 200 cc of pink fluid. The mediastinum showed numerous large and small air-filled blebs. The right auricle and ventricle were dilated. The right lung was edematous and its surface presented many subpleural blebs containing air. The left lung was collapsed, and several large subpleural blebs covered the surface of the upper lobe. The pathological diagnoses were hydropneumothorax, left, bronchiectasis, atelectasis and pneumonia, left lower lobe, emphysematous blebs, right and left lungs, pulmonary edema, mediastinal and subcutaneous emphysema, marked, and acute cor pulmonale.

CASE 7 D., a baby boy, was delivered by cesarean section at the Boston City Hospital at 10 15 a.m. on July 27, 1941. At birth the baby appeared normal, and exhibited no respiratory difficulty. During the evening of this day it was observed that his respirations were labored, and that he was cyanosed. Several attempts were made to aspirate mucus from the upper respiratory passages and trachea. Oxygen and carbon dioxide were administered by mask. Despite these measures, the infant died at 9 45 o'clock on the following morning.

At autopsy, performed 24 hours after death, upon removal of the sternal plate a large air-filled sac was encountered in the anterosuperior mediastinum, not communicating with the pericardium, and lying posterior to the thymus. This air sac measured 5 by 7 cm. Many smaller bullae averaging 1.5 by 2.0 cm. were found inferior to the sac and between the sternum and the pericardial cavity. Both lungs were atelectatic. Along the anteromedial aspect of the left lung were three small subpleural blebs. Air was found beneath the reflection of the pleura and the hilus of the left lung, communicating with the large air sac described above. Section through the hilar region of the left lung revealed "evidence of separation of the parenchyma from the vessels and bronchi by spaces which appeared to have contained air." The pathological diagnoses were atelectasis of the right and left lungs, interstitial emphysema of the lungs, and mediastinal emphysema.

CASE 8 A. B., a 26-year-old housewife, was admitted to the Boston City Hospital on November 20, 1947, because of pain in the chest and back of 4 days' duration. The pain had occurred suddenly, after the patient had bent over to pick up something and was described as severe, sharp and substernal, with radiation through to the back. It had persisted to the time of entry. No intensification was noted with respiration, but the pain was definitely worse in the left lateral recumbent position. Dyspnea had been present since the onset of the illness and was also aggravated when the patient lay on her left side.

During the three months prior to admission, the patient had lost 24 pounds in weight. For 1 month she had been bothered by a productive cough having raised about 4 tablespoonfuls of green never bloody sputum daily. Associated with her present illness were severe night sweats, never previously experienced.

On physical examination the patient appeared acutely ill, flushed and in marked respiratory distress. There was definite evidence of recent weight loss. Subcutaneous crepitation was elicited about the base of the neck and in the supraclavicular fossae. The trachea was deviated to the right. The left side of the chest was hyperresonant to percussion and the breath sounds were diminished to absent. Broncho-

vesicular breathing and fine moist rales were heard over the right upper lobe.

The temperature was 103.8°F, the pulse 140, and the respirations 38. The blood pressure was 118/80.

X-ray study of the chest after admission revealed an extensive pneumothorax on the left and soft, mottled, tuberculous infiltration involving the right upper lobe. Air was demonstrated beneath the left leaf of the diaphragm.

The sputum was positive for tubercle bacilli.

The patient was seen on the day of entry by the thoracic surgeon, who treated the tension pneumothorax at first by repeated aspiration and then by the insertion of an indwelling needle connected to a water seal. The dyspnea was markedly improved, and the chest pain gradually subsided. Throughout the hospital stay, the temperature remained elevated, varying from 99 to 102°F. A left pleural effusion developed, which on tapping yielded 800 cc of straw-colored fluid. On December 16 the patient was transferred to the Boston Sanatorium for treatment of the pulmonary tuberculosis.

CASE 9 H. D., an 18-year-old schoolgirl, was admitted to the Boston City Hospital on July 2, 1935. Five days prior to entry she had suddenly been seized by severe, sharp pain in the left side of the chest while at the dinner table. The pain was intensified by respiration, and was accompanied by dyspnea. She was under the care of her family physician, who finally referred her to the hospital, because of progression of her symptoms and difficulty in obtaining her pulse and blood pressure.

On entry she appeared critically ill, was in great respiratory distress and presented signs typical of tension pneumothorax on the left side, 1500 cc of air was removed immediately by aspiration, resulting in definite relief of her symptoms. On the following day there was evidence of left pleural effusion, but no tap was performed because of the marked improvement in the patient's condition. On July 21, however, 300 cc of straw-colored fluid was removed from the left side of the chest, and on July 31, 300 cc of bloody fluid was aspirated. A low-grade fever (maximum temperature of 100°F) persisted for several weeks, but gradually subsided with the resorption of the chest fluid.

The temperature was 97.8°F, the pulse 122, and the respirations 44. The blood pressure was 70/46.

X-ray studies confirmed the findings of pneumothorax and hydropneumothorax.

Guinea-pig inoculations performed on two occasions with the pleural fluid were negative for tuberculosis.

The patient was discharged on October 4, asymptomatic, and showing only the evidences of thickened pleura by x-ray study. The diagnosis was spontaneous pneumothorax with complicating hydrothorax and hemopneumothorax.

On February 26, 1938, approximately 2 1/2 years later, she was readmitted to the Boston City Hospital. She had been perfectly well in the interim, until the day prior to entry, when she noted the sudden onset of pain in the region of the left shoulder, radiating downward over the left posterior portion of the chest and axilla. The pain had occurred while she was walking down the street. Deep breathing and coughing aggravated the pain.

On physical examination the patient did not appear acutely ill or distressed. The lungs were essentially normal. The area over the sternum was hyperresonant to percussion, and cardiac dullness was obliterated. With the patient leaning forward the hyperresonance over the sternum was lost. Just to the left of the lower end of the sternum definite mediastinal crepitation was audible. This finding was confirmed by several observers. No subcutaneous emphysema was demonstrable.

X-ray examination of the chest on the following day revealed clear lung fields.

The course in the hospital was perfectly benign, and the patient was discharged on March 4, with a diagnosis of mediastinal emphysema.

A note received by the hospital from this patient in April, 1947, disclosed that she was in excellent physical condition, and that she had had no further recurrences of her former difficulties.

SUMMARY

A review of the pathogenesis and predisposing factors in the development of mediastinal emphy-

sema is presented, along with the signs and symptoms characteristic of the condition.

In view of the many factors, often overlooked, that lead to the development of mediastinal emphysema, it seems advisable to drop the term "spontaneous" in such cases.

Although the majority of cases pursue a benign course, one should always be watchful for signs of severe mediastinal compression, which may require mediastinotomy as a life-saving measure.

The common complication of tension pneumothorax requires measures to decompress the pleural cavity.

The possibility that many cases of so-called "spontaneous" pneumothorax, especially when left-sided, actually represent a phase of mediastinal emphysema, is pointed out.

Nine cases illustrative of various aspects of mediastinal emphysema are presented.

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NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-EIGHTH ANNIVERSARY (Continued)

House of Delegates, June 13, 14 and 15, 1949

Dr Sycamore moved that each county medical society be requested to take action similar to the action taken by the Cheshire County Medical Society, to appoint a committee of the staff to review the Blue Cross and Blue Shield admissions, and, secondly, that each hospital staff be urged to co-operate fully with Blue Shield, by appointing an active review committee, and that each county committee of the educational campaign be instructed to communicate with each hospital in the county to secure co-operation in this program

The motion was duly seconded

The Speaker then asked for a vote on the motion, which was carried

The Speaker asked for a vote on the second part of the motion — that each hospital staff be asked to co-operate fully with Blue Cross by appointing an active review committee. The motion was carried. The next part of the motion, that each county committee of the educational campaign be instructed to communicate with each hospital in the county for their co-operation in the program, was then put to vote and carried

Speaker Dube observed that the Committee on Medical Economics should bring up the question of electing or re-electing the officers for the Blue Shield

Dr Sycamore stated that it was the duty of the House of Delegates to approve the Board of Directors for the Blue Shield. He moved that the following officers of Blue Shield be approved: Leslie K. Sycamore, of Hanover, president, Hiram E. Upton, of Burlington, Vermont, vice-president, Charles R. Eastman, of Kensington, vice-president, Ray W. Pert, of Concord, treasurer, and Frank J. Sulloway, of Concord, clerk. The directors included the following: F. Ray Adams, of Springfield, Vermont, Right Reverend Monsignor J. S. Buckley, of Concord, O. E. Cain, of Keene, Laurence C. Campbell, of Barre, Vermont, Albert M. Cram, of Bridgewater, Vermont, Right Reverend Bishop John T. Dallas, of Lee, Harold Daoust, of Nashua, Francis J. C. Dube, of Center Ossipee, Fred Fernald, of Nottingham, Theodore H. Har-

wood, of Burlington, Vermont, John A. Hunter, of Dover, Elbridge E. Johnston, of St. Johnsbury, Vermont, Douglas Kitchel, of St. Johnsbury, Vermont, James M. Langley, of Concord, John Lawson, of Barre, Vermont, Roland McSweeney, of Brattleboro, Vermont, Frank A. Mahoney, of Bennington, Vermont, Carleton R. Metcalf, of Concord, S. Aldis Miller, of St. Albans, Vermont, J. J. Morin, of Rochester, Clinton R. Mullins, of Concord, George M. Putnam, of Contoocook, Allan D. Sutherland, of Brattleboro, Vermont, Roy D. Watkins, of Rutland, Vermont, and Isadore Zimmerman, of Manchester. R. S. Spaulding was named executive director.

This motion was seconded and was carried

The report of the Committee on Medical Education and Hospitals was then presented, as follows:

The chief activities of this committee during the past year have been in connection with the work of the advisory councils appointed by the State to consult with the Department of Health, which functions as the administrative agency in the operation of the Hill-Burton Hospital Act within the State, and an Advisory Board, which was made up of the same membership, to act with the Department of Health on new legislation in the field of hospital licensure.

The formulation of a State plan of hospitalization has been completed and is about to be published. The specific hospital projects within this plan have been delayed principally because of the problems of local finance and the uncertainty of costs. Although in the general field of construction it has been presumed that costs have stabilized themselves, there has been no large amount of substantiation of this supposition by the few instances where plans have been submitted for actual bid. It is believed that the progress in the field of the State hospital plan has been satisfactory and has been generally well accepted.

During the past year the Department of Health has conducted hospital inspections in conformity with the new laws regarding licensure. This legislation was designed to put more control in the Department of Health, particularly in relation to nonpublic institutions, which have been poorly controlled in the past, and fire hazards, medical supervision and so forth. The adoption of any regulations, which must be standard in their application, has brought perhaps minor irritations to some of the older and well established institutions, but it is to be remembered that reasonable uniformity in requirements are necessary to the carrying out of the whole program.

This committee believes that the Society should make an official effort to increase the enrollment of its membership at the New England Postgraduate Assembly. The

Assembly was held last year at the Copley Plaza Hotel, Boston, on November 3, 4 and 5, with a total registration of 804, of which New Hampshire contributed an enrollment of 49. This assembly, which is largely an effort of the Massachusetts Medical Society, has been of increasing value. Its sponsorship may ultimately come under the various New England state medical societies, a topic that has already been discussed before the Council of the New England State Medical Societies, if adopted, this plan would make the assembly a distinctly proportionate responsibility of the New Hampshire Medical Society. Meanwhile, efforts could be made among the county societies to inform the members of the value and the proximity of this program.

JOHN P. BOWLER, *Chairman*
JAMES W. JAMESON
HOWARD P. SAWYER

Dr Leonard, for the Committee on Officers' Reports, submitted a minor correction to the report backed by a list received from the chairman of registration of the 1948 New England Postgraduate Assembly. Inasmuch as this improves the position of New Hampshire in the roll call, a census of 55 instead of 49 New Hampshire doctors registered at the Assembly was reported. By New Hampshire counties, they were as follows: Hillsborough, 13, Rockingham, 11, Grafton, 7, Merrimack, 7, Strafford, 5, Belknap, 4, Cheshire, 4, Carroll, 2, Coos, 1, and Sullivan, 1. There were 24 doctors who went from the counties bordering on Massachusetts, 31 went from the other counties. Only 33 New Hampshire doctors attended the Assembly in 1947 so that the 1948 registration represented nearly double the former attendance.

Dr Leonard moved that the report of the Committee on Medical Education and Hospitals be accepted.

This motion was duly seconded and was carried.

The report of the Committee on Mental Hygiene was presented, as follows:

Two bills pertaining to commitment to the state hospital and nomenclature of forms to be used were passed. One, a voluntary act on the part of the patient, now requires agreement to a two-month period of treatment and a two-week period, after their request for release, prior to discharge. This permits a longer period of treatment, which in nearly every case is necessary to obtain the maximum benefit, because although the advanced type of treatment of shock therapy shortens the duration, the length of stay permits psychotherapy together with "total push" used with groups. Time is also obtained to complete a more intensive study of the personality traits in each case.

The second, on the regular form of commitment by two physicians, has finally permitted the doing away with the now obsolete term "insane" and allows the committing physicians to interpret emotional functional conditions of a severe or moderately severe nature, permitting a regular commitment. It also allows for the removal of the stigma of the terminology "insane," which the patients, as well as their relatives, disliked so much.

The State has been very fortunate in the fact that Dr. John L. Smalldon has become superintendent of the state hospital. He has brought to his duties years of experience in psychiatry and administrative ability so essential to this type of hospital. Under his leadership, those who work with him have already been definitely stimulated to intensified effort, not only on effecting cures in those already mentally ill but also to assist in promoting steps of preventing mental illness.

More and greater efforts must be made toward the prevention of this form of illness, for as the span of life

physically has been prolonged, we are perceiving an increase of anxiety or depressed states in the aging person due to various environmental factors. If reached early, a psychosis of severe nature may be avoided, and the necessity of hospitalization prevented. At the present time 44 per cent of admissions to the state hospital occur in persons over sixty-five years of age. Either steps to prevent must be found or else such an overcrowding will occur that some form of community hospital will have to be arranged for in each county.

From the hospital has emanated the development of outpatient clinics in Rochester, Portsmouth, Nashua, Manchester, Keene and Claremont. Soon we hope that clinics will be arranged for in Laconia and Berlin. Primarily, these are for follow-up work with patients sufficiently recovered to have returned to their homes, but they may be made available for cases referred by physicians when patients are in need of psychiatric advice and are financially unable to go to some psychiatrist in private practice. In addition, the Mental Hygiene Child Guidance Clinics under the director, Dr. Anna Philbrook, have been continued with admirable success, which might be further enhanced by increased personnel.

More adequate extension of the services of the mental-hygiene clinics in the State has been hampered by lack of adequately trained personnel. This in turn has resulted from the inability of the classification board that determines the salaries paid to various state employees to raise the minimum salaries for qualified applicants to equal that granted in other New England states. Unless a special effort is made to obtain an adequate staff for the clinics and the study home contemplated in former Governor Winant's residence, the entire mental-hygiene program will remain bogged down and become a program on paper only. The director of the Mental Hygiene Clinic will not be able under the circumstances to carry on alone as far as the psychiatric end is concerned, for the administrative duties will no doubt absorb much of her time, leaving little time for clinical work with patients. In view of the fact that part of the funds for the Mental Hygiene Clinics is of federal origin, this niggardliness in such an important program appears ill advised, especially when one of the aims of the Mental Hygiene Clinics is to prevent the need for hospitalization for future patients in the state hospital.

The Committee desires also to bring to your attention that during this past year the Department of Mental Hygiene and Child Guidance Clinics took another step forward toward its goal of establishing a study and receiving home. The home of the late Ambassador John Winant was purchased by the State for this purpose. The state program is now titled "Winant House, New Hampshire Mental Hygiene Clinics." The proposed use of the Winant house is for the diagnosis and treatment of emotionally disturbed children needing more careful diagnosis than can be provided in any existing outpatient clinic, thus helping to prevent delinquency and later mental illness. This service is provided for children needing a more extended period of psychiatric treatment, including those with diagnoses of psychosis, epilepsy, feeble-mindedness or needing long-term care. The Clinics moved from the Thayer Building at the state hospital on November 15, 1948. Since that time a full schedule of clinics has continued, in addition to planning with trustees and architects for remodeling. We have had interviews with applicants for positions such as matrons, caretakers, girls and boys as supervisors, nurses and teachers. The staff are very interested and enthusiastic about this project and have given much time and thought toward making sound plans for a program that will benefit many children and parents.

There are two buildings — the main house with twenty-five rooms and seven baths, and the kennel building, which has two four-room apartments upstairs as well as a large room with the same space downstairs. The main house will be used as a residence for twenty-five children and at first will be a combined unit for both receiving and study home. The building will require a minimum of remodeling and will give the children an environment that is homelike and not crowded. The children will be living in rooms that are large, sunny and pleasant, therefore sleeping arrangements will not be crowded. There will

be single and double rooms. The maximum will be four in a room. This will afford privacy, which is much needed for children who are emotionally disturbed. The kennel building will be the administrative building and will house the clinic staff and medical unit.

The thirty-two acres of wooded land will be ideal for children's picnics, hikes and nature study. There will be two playground areas, one for younger group and one for older children, as well as a swimming pool.

It is believed that this program can get under way well within the capital funds appropriated for this purpose.

From November, 1948 to March, 1949, 71 clinics have been held, 465 individual patients have been seen, and there were 525 total visits to the clinics.

The need for a state-wide program for dealing with alcoholism is an accepted fact. Many alcoholic patients would benefit from a judiciously executed program of physical and mental rehabilitation. At present much of the load is being carried by members of the state-hospital staff, for the admission rate for alcoholism has increased from 2 to 14 per cent of all admissions in the past year. There are plans proposed by the Board of Inebriates for the opening of a special hospital for the treatment of alcoholism in the State. This, besides entailing a high initial financial outlay, will also require a large annual budget for maintenance and with the mental-hygiene system in the State bogged down for lack of funds for qualified personnel, the advisability of proceeding with an expensive plan for the treatment of alcoholism should be given closer scrutiny before another white elephant is foisted on the taxpayer. It is suggested that an independent study be made of existing facilities for the treatment of alcoholism, and at least one psychiatrist and one other physician included in this board. The problem of alcoholism in New Hampshire differs considerably from that in other New England states or New York State. The incidence of alcoholism is less, and in view of the fact that in most instances the problem is psychiatric or psychosomatic, the advantage of having the treatment of alcoholism come under both the Department of Health and Mental Hygiene Clinics should be considered.

The last suggestion is that a law to be presented to the Legislature be sponsored and supported by the Society. This law would permit children under five years of age, who required treatment or care for mental deficiency, to be entered at the Laconia State School. At this time no facilities that are really suitable are actually available for such children, and many social agencies are at a loss as to how they can adequately care for these children, for the homes are very frequently entirely unsuited to care for them for obvious reasons.

The carrying out of such a law would also require the voting of sufficient funds to provide, at the Laconia State School, for increase of personnel and quarters for such children.

Finally every effort, from all sources, including social agencies, churches, mental hygiene clinics, psychiatrists in private practice and physicians generally should be directed toward the prevention of mental illness or at least its early recognition and institution of proper treatment to prevent a more serious condition from developing.

A. B. HOWARD, M.D.
SIMON STONE, M.D.
EDWARD S. MORRIS, M.D.

Dr Leonard, for the Committee on Officers' Reports, moved that the report of the Committee on Mental Hygiene, with its recommendations, be accepted.

This motion was duly seconded and was carried.

The report of the Committee on National Emergency Medical Service was then presented.

In the report submitted by this committee last year it was stated that plans and enabling legislation for civilian defense must be necessarily on a national level and that organizations on a local level must wait directives or orders from the Office of the Director of National Defense. In the interim time that report much thought and study

has been given to the problem by the Office of Civil Defense Planning. Chairman Russell J. Hopley of the Civil Defense Planning Board submitted a report to the Secretary of Defense in November, 1948. This report was 300 pages of text, was supplemented by 17 organizational charts and proposed model legislation on federal, county and local levels and is purchasable for \$100 from the Superintendent of Documents, United States Printing Office, Washington 25, D. C. In this report it was recommended that the Director of the Office of Civil Defense Planning should report to the Secretary of Defense or directly to the President. The former was thought to be preferable. Four deputy directors are provided for plans and operations, medical and health service and special-weapons, technical services and training. Under the general supervision of the medical and health services and special-weapons defense deputy director would be four broad divisions: medical and health services, radiologic defense, chemical defense and "other special-weapons defense," the last named concerning itself with a subject that is still alluded to only inferentially — biologic warfare. It was recommended by Mr. Hopley's committee that bureaus organized similarly would be set up by the several states, cities and metropolitan areas. It is recommended by your committee that no action on the recommendations of this report by Mr. Hopley be taken until the report has been studied by the Council on Medical Emergency Service of the American Medical Association and suitable directives from the latter promulgated. Because of growing interest in civilian defense and disaster planning and because the enormous impact of nuclear physics and chemistry with its attendant hazards has already shaped the size of things to come, it is believed that the attention of the members of the Society should be directed to two communications on this subject. One, entitled "Problems of Medical Care in the Atomic Age" by Harold Lueuth, M.D., appeared in the *Illinois Medical Journal*, for August, 1948, and another, entitled "Medical Care of the Nation in the Event of Another War," by James C. Sargent, M.D., appeared in the *Journal of the American Medical Association* of January 15, 1949.

A matter of grave concern to the nation during the past nine months is the critical shortage of doctors in the armed forces. In February the Armed Forces Medical Advisory Committee advised Secretary of Defense James Forrestal to start a drive to recruit four thousand doctors and dentists for the armed forces by December, 1949. That committee asserted that medical students who completed their studies while others were in uniform were under "moral obligation to serve now." The committee set up to advise Mr. Forrestal on medical needs of the armed forces termed the shortage of doctors and dentists critical. They asked the Secretary to begin a recruiting drive immediately directed toward 15,000 young men who were deferred in World War II in order to complete their professional training. The Armed Forces Medical Advisory Committee estimated that the armed forces would be short 1500 physicians and 1600 dentists by July 30, 1949, and 2200 physicians and 1400 dentists by December, 1949. This advisory committee is composed of members of the American Medical Association, representatives of the Surgeons General of the Army and Navy, and the Air Force Surgeon. Thus, there is civilian medical representation at this high-policy level of the Government whose aim will be to safeguard the interests of the public, the armed forces and the medical profession. This committee wishes to point out to prospective volunteers for the armed forces that the Medical Administrative Corps has been expanded so as to leave doctors more time for medical duties and to relieve them of paper work. An additional stipend of \$100.00 per month is being paid to medical officers who volunteer for active duty prior to being called for induction. Training opportunities and career-guidance plans have been developed. Intensified research programs have been activated. Numerous other changes effected make service in the armed forces a more valuable professional experience than has heretofore been the case. It can safely be predicted that the doctors needed by the armed services will be obtained one way or another and if it is not done on a voluntary basis it will be done compulsorily. This committee reiterates this year its belief that young physicians who derived all or a part of their medical education

from the Army ASTP program or the Navy V-12 program and who have not already served on active duty should be the first group of physicians to volunteer for active duty with the armed forces. On December 12, 1948, President Sensenich of the American Medical Association addressed a letter to these young doctors urging them to volunteer for service in the armed forces. Of the physicians under the age of twenty-six years who were written to, only 500 requested application blanks for a commission. This, of course, was very short of the anticipated number of requests for commissions. There were a total of about 8000 such doctors whose education was provided for by the Government under ASTP and V-12 programs. In March Secretary Forrestal sent a letter to each of these men urging them to volunteer immediately for active duty in such numbers as to allow replacement of medical officers now on active duty who have had two years of active duty following ASTP or V-12 training.

Your committee strongly supports the program of the Government to recruit doctors for the armed forces and urges doctors who have served little or no time on active duty to volunteer now.

DANIEL J. SULLIVAN, M.D.
CLARENCE E. DUNBAR, M.D.
JOHN C. ECKELS, M.D.
JOSEPH M. MCCARTHY, M.D.
BERNARD J. MANNING, M.D.

Dr. Leonard, for the Committee on Officers' Reports, moved that the House of Delegates place on record the following statement and instruct the Secretary to transmit it to each member of the Society and to the press: "The House of Delegates, as the representative governing body of the New Hampshire Medical Society, believes that the increasing needs of the armed forces place a moral obligation upon the young physicians in the Society who derived all or part of their medical education at the expense of the Government and who have not yet served on active duty." He also moved that the Report of the Committee on National Emergency Medical Service be accepted.

After some discussion the first motion was carried.

Dr. Leonard then moved that the Report of the Committee on National Emergency Medical Service be accepted.

This motion was duly seconded and was carried.

The report of the Committee on Public Health was then presented, as follows:

The Committee has been active in the various hearings of public-health bills introduced into the current session of the General Court.

Senate Bill No. 7, an act relative to the practice of physiotherapy, received careful attention, and considerable time was spent on its investigation and on presentation of arguments against the original wording of the Bill. It was believed that such freedom as the Bill provided the physiotherapist would materially jeopardize the accepted standards of medicine in New Hampshire.

Other bills affecting the public health were also given attention in form of consultations, appearance at hearings and personal conversations.

Owing to the extensive attention given to medicine by the 81st Congress it was thought wise not to promulgate any considerable changes in the present public-health organization within the State. Letters have been written to the New Hampshire delegation in Congress, and personal interviews were held with two of the members. Assurances were given that everything in their power would be done to thwart any measures conducive to the lowering of medical practice or the altering of the physician-patient system.

DONALD G. BARTON, Chairman

Dr. Leonard, for the Committee on Officers' Reports, moved that the report of the Committee on Public Health be accepted.

This motion was duly seconded and was carried.

Dr. Leonard then moved that the sum of \$100.00 be contributed to the Council of the New England State Medical Societies.

This motion was duly seconded and was carried.

The report of the Committee on Tuberculosis was presented.

The participation of our country in World War I was but a few years ahead when the Society authorized the formation of this committee. In that year, 1914, tuberculosis was close to the top of the list among the leading causes of death throughout the nation and in the State. The death toll from tuberculosis in New Hampshire was over 500 annually, and the death rate 114 per 100,000 population.

The intervening years have witnessed increasing development and acceleration of knowledge, equipment and facilities to control the disease throughout the nation and in the State. Tremendous progress has been made, and the gains that have been achieved in reducing the mortality and morbidity of tuberculosis cause many tuberculosis workers to speak hopefully of the possibility of actual eradication of the disease in fifteen to twenty-five years. The more conservative among us estimate a period of approximately fifty years for complete eradication of tuberculosis in the United States, assuming continued intensive efforts for control and eradication, and barring the occurrence of unfavorable factors such as serious depression, widespread unemployment and resultant inadequate nutrition for great proportions of the people.

The progress in the control and toward the eradication of tuberculosis in New Hampshire is particularly gratifying. The 1914 toll has been reduced to 85 deaths in 1947 and a rate of 15.5 per 100,000 population and in 1948 to 68 deaths and a rate of 13.1. New Hampshire has the lowest mortality rate of any state east of the Mississippi River, and stands fourth in the nation. Since 1915 the decline in the tuberculosis death rate in New Hampshire has been the greatest in the nation, being approximately 87 per cent. This encouraging record is particularly gratifying in view of the fact that the State is the second most highly industrialized among the states of the nation in proportion to population.

We believe it is a most laudable ambition, and within our possibilities, for New Hampshire to increase the effectiveness of its campaign to the end that the State may be the first among the states of the nation to win the goal of complete eradication.

The phenomenal gains that have been won and the promising outlook for the ultimate eradication of tuberculosis are due in large part to the whole-hearted co-operation of physicians, nurses, other professional workers, tuberculosis patients and the people in both governmental and voluntary capacities in the efforts for control and eradication.

Throughout the years the Committee on Tuberculosis has endeavored to stimulate the interest and enlist the active support of members of the Society in the campaign for control and eradication. It has also endeavored to give all possible assistance to members of the Society in providing services for the early discovery of tuberculosis among their patients and in the families of their patients. The entire facilities of the chest clinics throughout the State, with resources of chest x-ray examinations, tuberculin tests and tuberculosis nurses' services, have been placed at their disposal. These facilities have been utilized by the physicians to an increasing extent, more particularly during the past five years, not only for checkup on known and suspected cases but also for the examination of contacts.

Probably in no other state in the nation is so large a proportion of the physicians participating actively in the program for discovery and prompt supervision and treatment of tuberculosis. There is good reason to believe that

this is the deciding factor in the phenomenal reduction in tuberculosis mortality and morbidity.

Our sanatoriums have contributed greatly to the reduction in the death rate from tuberculosis. Yet it is found that a large number of active cases are under supervision and treatment in homes. The increasing use of chest surgery, particularly thoracoplasty, has contributed materially to the number of cured cases in many parts of the State.

Within the past year the Department of Health has obtained a traveling chest x-ray unit for mass x-ray examinations. This unit is designed to provide chest x-ray studies for large numbers of people upon an industry-wide or even community-wide basis. It is emphasized that if everyone received such an examination all cases of tuberculosis would be discovered. However, there is much more to such a program than mere x-ray examination. If such a program is to be a success, much preliminary work must be done in the industry or the community before the films are taken so that most, if not all, of the people respond. Equally important, after the taking of the x-ray films adequate follow-up work has to be done to determine which cases are clinically active. Many films show shadows suggestive of tuberculosis, when no clinical disease is present. Experience reveals that in a state with a low mortality and morbidity from tuberculosis, such as New Hampshire, a considerable percentage of the films showing shadows suggestive of tuberculosis are found to be those of well nourished persons who are free from symptoms. These are usually cases of spontaneously healed tuberculosis. Yet the discovery of hitherto unknown active cases can hasten the goal of eradication. It must be remembered that it is also possible for chest x-ray films to appear normal in some persons in whom active clinical tuberculosis is present, since approximately 25 per cent of the lungs is hidden by the bony framework of the chest and the chest organs. There are also certain dangers that must be recognized if the full value of the x-ray survey is to be obtained. One of these is the average layman's belief that if his x-ray film is normal he does not have tuberculosis. Another is that one negative chest x-ray examination means that the person will not have tuberculosis in the future. Both conclusions are sadly erroneous. It cannot be too strongly emphasized that although chest x-ray examination is a distinct aid in the diagnosis of tuberculosis a definite diagnosis should not be made from the x-ray film alone, nor is it always possible to rule out tuberculosis on that basis alone. All the resources for diagnosis such as history, physical examination, sputum examinations, gastric lavage and sedimentation rate, may be needed to establish or rule out a case of clinically active pulmonary tuberculosis.

The traveling unit of the Department of Health provides a 70-mm film. This is the screening process. When the suspicious cases are found the 70-mm film must be followed up by a standard 14-by-17-inch film. However, as has been said before a film of any size must be considered as a diagnostic aid to be used in collaboration with all other resources to establish a definite diagnosis.

The success of a mass chest x-ray survey depends upon adequate follow-up study of all suspicious cases. This is a real responsibility. Failure to meet it can ruin the entire program. The responsibility rests largely with the general practitioner. Here in New Hampshire as elsewhere, the Department of Health refers patients with suspicious shadows upon the films to their own physicians. In many cases responsibility has been accepted and serious effort made to establish a definite diagnosis, and to facilitate prompt and adequate treatment. In some cases duty has been shirked, and occasionally x-ray reading has been given to the patient with indifferent advice about follow-up study.

Our experience with the tuberculin test convinces us that it will play an important part in the final eradication of tuberculosis. This test is most valuable when the death rate is low and there are comparatively few reactors. It is more significant after the death rate has been reduced and there are comparatively few cases to be found. The mass x-ray surveys are most useful when the death rate is high and the incidence of positive tuberculin-test reactors is high. The percentage of positive reactors to the tuberculin test among the young people of high school

age in New Hampshire has been reduced from approximately 60 twenty-five years ago to about 10 at the present time. It is not a large undertaking to test all children of school age. A child who presents a positive reaction should be considered a potential case of clinical tuberculosis and kept under supervision.

Of equal importance, search should be made for the source of infection in the families of positive reactors in children. The younger the child, the more likely it is that the source of the infection is in the immediate household. In 2 recent cases of positive-reactor children, the mother in one, and the father in the other were found to have active pulmonary tuberculosis, with tubercle bacilli in the sputum. The co-operation of the parents in both cases was brought about through the interest and active part taken by the family physicians.

It should always be remembered that tuberculosis is present as much in the older age group as in young persons. The older people deserve more attention and need more checkups for tuberculosis than they are receiving now and are often the source of infection of younger family members or associates. The coughing grandmother taking care of the baby is frequently the cause of tuberculous meningitis.

Many advances have recently been made in the treatment of tuberculosis. Surgery has played an important part, and has taken a high place in treatment. Several years of use of streptomycin and other antibiotics have served to demonstrate their advantages, disadvantages and limitations in the treatment of tuberculosis. It is possible that in the future some antibiotic may prove to be the long-sought cure.

In this report the Committee has sought to present a brief outline of our present position in the fight against human tuberculosis in New Hampshire, our objectives, and an appeal for the continued whole-hearted participation of our membership. For the success of the program for control and eradication a large measure of credit and appreciation is due to the physicians of New Hampshire. If the future program for eradication is to function at its best, it must be recognized and accepted by the general practitioner that no plan can be a success without his assistance and co-operation.

The Committee urges the continued and increased use of the chest x-ray examination by physicians in their general practice and in the hospitals. We also urge the wholehearted co-operation of the members in the mass chest x-ray surveys of the Department of Health. Particularly do we urge prompt follow-up study by the physician of all persons whose chest x-ray films show definite or suspicious shadows. Every resource should be utilized by the members to establish the presence or absence of clinically active pulmonary tuberculosis in these cases.

We hope for the continued wholehearted co-operation of the members in the tuberculin testing of the school population of the State to the end that all potential cases may be found, as well as the patients with possibly active "open" cases who may be the spreaders of the infection among them.

ROBERT B. KERR, M.D.
FRANK G. SELDON, M.D.
JOSEPH D. SPRING, M.D.

Dr. Leonard, for the Committee on Officers' Reports, moved that the report of the Committee on Tuberculosis be accepted.

This motion was duly seconded and was carried.

Mr. Angus B. Woodbury, for the Committee on Public Relations, then described the campaign in New Hampshire against compulsory health insurance.

The Committee on Public Relations met on March 13, 1949, and determined to put in force some plan to counteract growing interest in President Truman's compulsory health insurance legislation.

The Angus B. Woodbury advertising and public-relations agency was consulted and subsequently engaged to carry out the Society's educational and informational campaign.

Action was immediate. The agency prepared releases for newspapers and radio stations announcing plans for the campaign. At the same time a representative of the Woodbury firm was assigned to the task of organizing "co-ordinating committees" throughout the State.

The immediate objective—to organize and to publicize—was carried out with dispatch, and within ten days the people of the State were aware that the doctors intended to broaden medical services and urge greater patient-physician participation in voluntary health care plans as the best assurance against compulsory health insurance or socialized medicine.

An organizational plan written by the agency was put into actual operation in every county. By the end of the first month these various committees were quite well organized.

Spearheading the New Hampshire campaign was an extensive publicity effort, which at the end of three months had resulted in the publishing of some 1500 column inches of copy. Had this been purchased at ordinary newspaper advertising rates, the total cost to the Society would have been approximately \$13,000. Owing to the news value of the releases prepared by the agency and submitted to the newspapers, editors found reader interest in them, and this extensive publicity was obtained without cost.

Co-ordinated with the publicity part of the public-relations program was a speaking schedule. The agency was able to enroll support of several prominent citizens, who, along with the campaign staff, have filled more than 50 speaking engagements throughout the State. It is conservatively estimated that between 4500 and 5000 people have heard some of our speakers outline the danger points of socialized medicine.

We have speakers scheduled through July 11.

Upwards of 20,000 pieces of literature have been distributed, most of it personally to members of county "co-ordinating committees" by the campaign staff.

Extremely close contact has been maintained between the Society's public-relations counsel and the various voluntary health care programs, particularly Blue Cross and Blue Shield.

Owing to the liaison established and developed, there has resulted an obviously increased and improved relation between the Society and the county societies, the pharmacists, nurses and hospital units. We cite the Cheshire County Medical Society proposal as the best example.

On at least three occasions the New Hampshire Medical Society has been publicly complimented for having one of the best organized and most effective campaigns against socialized medicine in the country.

A worthwhile and efficient organization has been built up in New Hampshire. It has now begun to function well, but each organization or "co-ordinating committee" is aware that much still remains to be done if the defeat of socialized medicine is to be accomplished.

This civilian and professional organizational effort ought to be continued, developed and enlarged as the occasion demands.

The effort put forth in this state has resulted in more than 4500 individual letters to the congressional delegation in Washington and to the President, in opposition to socialized medicine, as a result of such overwhelming public opinion, the delegation has committed itself to oppose compulsory health insurance legislation as currently proposed.

Maintaining status quo will not be enough.

Actually only a small percentage of the people of the State have yet expressed themselves on this all-important national issue. Much educational work remains to be done.

It is known that there are at least half a dozen "health bills" before Congress, any one of which might be pressed for adoption as an Administration measure. True, Senate Bill No. 5, and its House counterpart, No. 783, are accepted as being the "Truman plans." However, should public opinion change nationally, congressional sentiment, which now seems to be in favor of voluntary rather than compulsory insurance might change—perhaps overnight. The best assurance against subterfuge is a strong, continued and active campaign.

Through this educational campaign effort, the physicians have stepped up their public relations to a point of favor

in the eyes of the press as well as the general public. Good relations through public relations ought to be maintained as a safeguard, not only in opposing socialized medicine but also in furthering voluntary health care.

To date, the Society's three-month campaign has been effective and therefore successful. It has made it possible for more New Hampshire people to understand better the dangers of compulsory health insurance than was anticipated last March.

The campaign has been an affirmative one in that out of it has come something constructive—the Cheshire County Medical Society plan being a case in point.

The total estimated cost is \$2899.93.

Hearings have already started in the House and Senate on the hodgepodge of national "health bills." These hearings are being closely watched by the American Medical Association. Somewhere in this maze of social-reform measures will be found legislation with a preponderance of compulsion attached to it. Just what form and character legislation will take once it clears either House or Senate subcommittees is as mystifying as the reason why the President still insists on compulsory health insurance without a public demand for it.

But, politics being a continuing guessing game, neither the American Medical Association nor individual state medical societies can afford to lower their guard to a point of being ill prepared to meet social schemers in their whims about medicine. The only real answer, obviously, is to keep organizations active.

Subcommittee hearings, such as are now going on, can be lengthy affairs. They can be adjourned without prior notice. They can be postponed if it appears politically expedient to do so. They can be stepped up or abandoned.

Health measures, including compulsory health insurance, could be tossed into the full committee—either in the House or Senate—tomorrow. This probably will not happen, however,—and for several reasons.

President Truman, it must be remembered, has told the American people that he thinks they need, want and must have Government-controlled medicine. For some reason yet to be explained, he believes that there is a people's mandate for compulsory health insurance. There is no such mandate.

Mr. Truman and his leaders, failing to find it expedient to force compulsory health insurance now or before Congress decides to go home for the summer around August 1, can well wait until the second session of the 81st Congress is called back into session next January—or sooner.

Before compulsory health insurance, as now proposed, is either brought out for debate in Congress or relegated to the ash pile where it rightfully belongs, there will probably be some real old-fashioned horse trading.

It is reasonable to assume that either Mr. Truman or Congress may "give" a little to get this national health issue off the hook. When this "giving" starts, that is the time to watch out.

If Congress goes home by August 1, or shortly thereafter, without taking action on "socialized medicine," the Administration will undoubtedly go to work this fall to "educate" the people as to why compulsory health insurance should be a must on the agenda for the second congressional session.

Such a campaign—the Government has sponsored similar ones before—would have no holds barred. If the Society should weaken to a point of feeling "self-satisfied" by that time, it would be a major mistake.

It should be remembered that the Administration will continue its campaign for social reforms this fall, whether Congress is in session or not. Then, when the nation's lawmakers come back next January, Washington will have cleared some of the legislative decks to place "socialized medicine" before the people.

Thus, 1950 is certain to be a year of promise.

Either the President and the Administration will keep their promise to get through compulsory health insurance legislation, or the medical profession will keep its promise—and see that compulsory health insurance dies a just death.

Already, as Congressman Hugh Scott pointed out in his talk at Concord a few weeks ago, overtures are being made to make this whole issue of the "nation's health" a political football in the elections in 1950.

The American people must be kept alert to the dangers of socialization, especially this attempt to take away the freedom and individual initiative known so well to prevail in the medical profession. Such alertness will come about only through continued education and information effort, a responsibility already assumed by America's physicians.

Too much effort, downright energy and serious thought have gone into this campaign of the New Hampshire Medical Society's to be cast aside now that the first taste of a rather negative victory has been so pleasing.

If the old adage is true, and "nothing succeeds like success," looking ahead to more than partial victory regarding this national issue of compulsory health insurance may well be expected.

The doctors know what red tape, Government forms and political control would mean to the medical profession. The people are beginning to know too. A continuing campaign should practically assure defeat of compulsory health insurance in 1950.

But, as the president of the Society, Dr. Clarence E. Dunbar, has so well stated, a continuing public-relations program will do more than help defeat compulsory health insurance. It will help in furthering the doctors' efforts to broaden voluntary health care programs that in themselves offer the best assurance against socialized medicine.

A broad state-wide organization, composed of physicians and lay people, has been developed with a view toward carrying on an extensive educational and informational campaign.

This organization should now be subdivided into small community groups—in cities by wards and in counties by towns.

An effort should be made to make this a "public" campaign for the remainder of 1949 and in 1950. From the co-operation already received from civic and professional groups, such an objective is not impossible of attainment.

Organizational units and subunits can be created and developed immediately, adopting as their project broader medical services, as well as greater understanding and participation in voluntary health care through education. And this whole endeavor can be under the sponsorship of the New Hampshire Medical Society.

Large quantities of literature are available and can be used as "hand-out" material in every ward and town in the State. This has not yet been done, obviously owing to the high gear in which the previous campaign was turning. But it should be done and is recommended as a part of an extended campaign.

In connection with this effort will be the development of an inter-town and inter-city speaking schedule. Every community has within its borders certain people who enjoy taking the public platform on some subject of national importance. Already, our files contain the names of several people who would be willing to take part in such a program.

As much as possible, future organization should be composed of lay people, all working under the technical guidance and assistance of state and county medical society officers. This will make for less close supervision on the part of busy physicians and more responsibility and general program maintenance by the New Hampshire Medical Society's campaign headquarters staff.

There should be a wider distribution of the now well known picture "The Doctor." Quantities of this print are available, and it is recommended that the Society consider as a part of the extended campaign the possibility of using state-wide window displays. These displays would be made up by the campaign staff. In this manner, thousands of people would have a first-hand opportunity to "see" what the educational campaign is all about. Such an effort would also add to the effectiveness of the individual "community" organized campaign.

During the summer and fall months of 1949 considerable emphasis should also be placed on stimulating the educational and informational effort to include appeals to approximately 1,000,000 summer visitors.

Building organizations to enable the combining of local and summer visitor interest will go a long way toward getting a double value through a single effort. This plan ought to be carried out in the seacoast resort areas and the lake and mountain sections, where county organizations already in existence could easily be expanded.

The continuation of a state-wide speaking schedule will be an important part of an extended campaign. This effort has proved so effective during the past three months that broader development of public speakers will be of invaluable assistance. This phase of the campaign, of course, would be carried on by the campaign headquarters or public-relations counsel.

Obtaining qualified speakers, making arrangements, scheduling dates and such related functions are to be considered as a part of the broad program.

It must be apparent to all members of the Society that publicity has played an important part in the success of the state-wide effort thus far. In an extended program, the emphasis would obviously shift from organizational publicity to the developing of more educational material and announcements of new ideas for broader medical service and participation in voluntary programs. Then, too, it will be a part of any new program to extend an educational effort to include as much free radio time as it will be possible to obtain. As in the past, publicity for all weekly and daily newspapers will be carried out.

In the broadening of organizational work there will of necessity be a need for greater liaison between the Society and the general public, schools, colleges, industrial plants, theaters, stores, allied professional groups and professional workers. This would be a part of the extended campaign.

In the developing of new ideas for greater medical services and more extensive participation in voluntary health care programs, it will be necessary for the Society's public-relations counsel to work closely with the Society officers and many of the units mentioned above.

Distribution of literature to all the people of the State will be a part of the extended campaign. This will include an effort to get literature to all organizations, industrial plants, men's clubs, women's groups, veterans' organizations and professional groups. Owing to the time limit involved distribution to date has obviously been only spotty. There ought to be a concentrated effort literally to cover the State between now and early 1950.

Depending somewhat on the outcome of current compulsory health insurance legislation, it may be necessary for the Society's public-relations counsel to aid in working closely with national and state legislative leaders during the legislative session of 1950, or in New Hampshire, the proposed fall session of the Legislature.

It is proposed that during the extended campaign, the Society's public-relations counsel develop a working arrangement with the many New Hampshire service organizations such as the Lions, Kiwanis and Rotary. This would be for the purpose of filling speaking engagements and distributing literature, and for obtaining resolutions against socialized medicine for the next legislative period.

During the past three months the campaign headquarters had several requests for information from school units. This leads us to believe that in the extended campaign an effort ought to be made to provide schools and colleges with educational material and to assist them in carrying on talks involving the health program.

Consideration should be given to the possibility of developing a motor-corps unit in the Woman's Auxiliary. Such a unit would be most effective when compulsory health insurance legislation is reported out of the full House and Senate committees. A motor corps traveling around the State would stimulate and arouse people to the point of writing to congressmen in opposition to compulsory insurance. This could be made a very effective part of the campaign if it becomes necessary to use it.

Dr. Leonard, for the Committee on Officers' Reports, moved that the report of the Committee on Public Relations, as presented by Mr. Woodbury, be accepted, and also that the Committee on Public Relations contract for the continuation of the educational campaign in New Hampshire.

This motion was duly seconded.

President Dunbar stated that the whole question was bound up with the matter of raising the dues—whether an executive assistant to the Secretary.

die right away, but hangs on for two or three years. She has two or three nurses at home, as well as hospital bills, so that the bills amount to around \$20,000 to \$25,000, which wipes out his entire savings. Now, that doesn't happen very often. It is not always cancer, sometimes it is some other devastating disease, requiring constant care.

I have talked to the Blue Shield men, and they think if they were given adequate safeguards against abuse, they could underwrite catastrophic illness policies at a very low premium. Mr. Spaulding thought, for a wild guess, that something in the neighborhood of \$5.00 a year would take care of it, provided they were safeguarded against abuses.

That is one of the big arguments of the public, and, although it doesn't happen very often, it becomes very widely known.

And, by the way, we got these points from the public, they did not come from the medical profession. Mr. Shea, head of the AFL Electricians of New Hampshire, brought these salient features before us, and we are very much indebted to him.

We find that many people are complaining that although they pay for Blue Cross and Blue Shield coverage, when they go into the hospital, they find they still owe \$100.00 or more, depending upon the fees charged. The Blue Cross has been paying around 90 per cent of the bill. The surgeons send them a bill for \$150.00, the anesthetist costs \$25.00, and the assistant a little more. So that after he is paid by Blue Cross he still owes \$100.00.

We propose for wage groups (and we should settle that point this morning) that earn \$2500 that the medical profession go on record so that the insurance company can sell to the public, saying, "We will cover you entirely," and accept the indemnifying fee as the final fee for those in that wage group.

Now, with the people who earn more money than that, the surgeon and other physicians connected with the case are perfectly free to accept whatever extra charges they think the traffic will bear.

But we should like to be able to guarantee the general, average man with a family that after he pays the fee for Blue Shield and Blue Cross, his worries, financially, are over.

I don't think that we need to go into the other point, of solving this problem of over-hospitalization and the taking up of grievances with the public. I think that that was well covered last night.

Dr. Sycamore stated that when the plan had originally been set up, it was debated whether it should be made a service contract, with a definite income limit, which has some complications that are a little difficult to administer that could perhaps be avoided by agreement among the members that, in effect, a service contract could be made if fees were equal to the scheduled benefit. No exact income limit was ever set. He believed that such a limit should be set and the agreement made a little more specific. In the plans that have a service contract with income limit, there is quite a wide variation in that limit. The average on most of the plans in comparable areas is around \$3500 for a family.

He suggested that the principle of a service contract up to a definite income limit be approved, by acceptance of the benefit schedule as a fee schedule, and that it be left to the Committee on Medical Economics and the Board of Trustees of the New Hampshire-Vermont Physicians' Service to set that income limit, after appropriate study.

Secretary Metcalf asked if there were any difficulty in determining a man's income.

Dr. Sycamore replied that that was one of the problems, and was the reason why the benefit schedule had not previously been approved. There was an increasing tendency to charge over the schedule, even in low-income cases, and it might be necessary to put the new schedule into effect, to protect the subscribers.

Dr. Walck asked who was to determine the income bracket into which the subscriber belonged. In Strafford, the doctors voted on the principle of the Cheshire County Plan, but they would have nothing to do with determining the group in which the subscriber belonged.

Dr. Jessup stated that many patients were operated upon, basically on the recommendation of the internist, and yet the surgeon was the only one qualified to receive payment. He believed that the internist, who actually did most of the work, was entitled to something. He did not think it fair that the patient should pay it.

Speaker Dube stated that the question raised could be answered by the fact that some patients had only surgical and not medical coverage. Blue Cross was the hospital plan, and the doctors had nothing to do with that. Blue Shield, of course, had both surgical and medical coverage, but, if the patient had surgical coverage only, he did not get the medical reimbursement.

Dr. Brown observed that there was a similar situation in regard to obstetrics and the prenatal and postnatal care that is rendered.

Dr. Sycamore moved that the principle of a service contract in the lower income group be approved, that the level of the income covered and the mechanism be worked out by the Committee on Medical Economics and the Board of Trustees of the New Hampshire-Vermont Physicians' Service, and that the conclusions be studied by the groups concerned and reported back to the next meeting of the House of Delegates.

The motion was then duly seconded and was carried.

A supplementary report of the Committee on Medical Economics, which had been turned in on the previous day but had been held out for consideration, was then presented, as follows:

As the Blue Shield movement has assumed an increasingly important place in the field of medical economics, it has become increasingly obvious that a national agency was necessary to make possible the handling of contracts for national employers and widely scattered groups such as large labor unions. A year ago, a co-ordinated program was developed for Blue Shield and Blue Cross to establish a national enrollment and insurance agency. This proposal was submitted to the House of Delegates of the American Medical Association at its interim session last November, but was not approved.

Associated Medical Care Plans, the national organization of Blue Shield Plans, then proceeded with plans for a national Blue Shield agency independent of Blue Cross. This proposal, also, was submitted to the House of Delegates of the American Medical Association, through the Council on Medical Service, at its session last week in Atlantic City. The Council, believing that the Associated

Medical Care Plans had grown to the point of being able to stand on its own feet, recommended that there should be complete separation between the American Medical Association and the Associated Medical Care Plans, and that Associated Medical Care Plans should be free to proceed according to its own best judgment in dealing with its own problems. These recommendations were duly approved by the House of Delegates.

As a result of this action by the Council on Medical Service and the House of Delegates of the American Medical Association, Associated Medical Care Plans has requested each member plan to approve or disapprove the proposals for a national enrollment and insurance organization, and to submit the proposals also to its sponsoring medical society. The directors of the New Hampshire-Vermont Physicians' Service have approved these proposals. The House of Delegates of the New Hampshire Medical Society, meeting in special session last October, approved the plan for a national Blue Cross-Blue Shield Agency. It is therefore the recommendation of the Committee that the House of Delegates approve the principle of a Blue Shield National Service Agency.

LESLIE K. SYCAMORE, M.D., *Chairman*
J. C. DUBE, M.D.

Dr. Leonard, for the Committee on Officers' Reports, moved that this report be accepted, but did not feel like making any recommendation, in the hope that the motion would be made from the floor.

Mr. Spaulding stated that the new scheme of separation seemed to have stirred up some doubt that the national medical group had. He believed there was no question that it would help in holding or getting back some of the people lost, so as to provide the same benefits everywhere.

Dr. Leonard moved that the report be accepted.

Dr. Johnston asked if everybody present was aware that several organizations are very much opposed to this move, especially the organizations in the Pacific Northwest.

Dr. Sycamore briefly indicated the way that this national program would function, as follows:

There would be, in the first place, no interference at all with the local program of any plan. In case of enrollment of a national group, each plan would supply what its particular policy offered, and then if there was further coverage desired by the national group, the national plan would supply that additional coverage on an indemnity basis.

The whole purpose, of course, is to make it feasible to enroll large groups as a unit, which is what the employer wants, if he has plants in various states, he wants to make one agreement, and have one uniform contract, and not have to deal with different contracts in different areas.

The objections that have been raised have come mostly from the Pacific Northwest, as Dr. Johnston has said. And certainly, they do not represent the opinion of the majority of either the plans or the medical societies that voted the approval, which was something like 175 to 12. It is believed that this is an essential part of the voluntary prepayment program. The actual mechanism of setting it up is something that we do not need to go into here. The House of Delegates of the American Medical Association did not attempt to go into the details of the program, they merely accepted the principle of it.

If we have a national program, it would be easier for the Government to take it over, but that is not the way the Government works. When they have set up any program, they have their own administration, and any compulsory government insurance here would be under the Social Security Office, and it would not be a question of taking over.

We had a recent example in British Columbia, when the Provincial Government adopted the program, and the Blue Cross Plan just went out of business.

So that I don't think that is a valid objection.

I think the main objection is that we might as well have a Government bureaucracy running us as a medical bureaucracy.

Well, I think there is quite a difference between being run by our own elected representatives, who know our own problems, and being run by Government officials.

Dr. Dye asked if there would be disagreement between certain segments of working men who belong to a given group in New Hampshire and another group in Michigan, who are under the same company-coverage plan, with different benefits in different states.

Dr. Sycamore replied that that was the reason for the national program: additional coverage would be given when necessary.

Dr. Leonard stated that the motion implied that the supplementary report of the Committee on Medical Economics be accepted and not that it carried with it the approval of the House of Delegates to the questions raised in the report.

There was a chorus of "ayes," and the motion was carried.

Dr. Sycamore then moved that this House of Delegates approve in principle the establishment by Associated Medical Care Plans of a national service agency.

Dr. Leonard asked whether that included the previous Blue Cross and Blue Shield and the combined health services.

Dr. Sycamore answered that this was a Blue Shield proposal, disassociated from Blue Cross.

Dr. D. G. Smith stated that he had asked a number of times why the proposed national enrollment insurance agency was not approved last December. Strafford County had been quite upset to think that the American Medical Association did not approve of the plan. Some of the reasons given at that time were that any attempt to set up uniform premium rates, uniform benefits and uniform policies would meet with failure, because hospital rates and surgical fees are not uniform throughout the United States, and cannot easily be made uniform, the demands for services are not uniform, nor are the social customs and the wage scales.

What labor was trying to do through its demands on Blue Cross and Blue Shield to establish uniformity was actually to prove that the voluntary plans are a vehicle for forcing the Government social reforms on the population.

Another reason given was that a complete service policy for everyone in the population, without regard to income level, could not be provided. A central fund of \$500,000 was not enough to equalize the differences between the policies in the various states.

There was also the idea that federal subsidies would be utilized for the poor risks, the chronic and

the medically indigent. The fear was that if the Government subsidies came in, it would be only a short time before the federal Government took over the plans. Some of these ideas were in opposition to the national insurance agency, but Dr Smith thought they could be straightened out and overcome. But the opinion was that it would be quite a problem to get such a company on a sound footing, and further, that the American Medical Association did not want to go into it and form an insurance company.

Dr Sycamore asked why the principle had been approved at the last session.

Dr Smith replied that a definite need for such an organization was felt so that there might be checks on the medical profession and so that the plan could be made to work. The fear that the federal Government would take over still existed.

Dr Sycamore pointed out that at the last session of the House of Delegates, the American Medical Association did adopt a resolution, first separating the A M C P from the A M A and then approving a national program by A M C P, on the Blue Shield level, and not on the combined Blue Cross and Blue Shield plan. When the Blue Shield was put out, it was put out with the principle that the low-income group would be helped to meet the economic tragedies of illness, if this program was for the purpose of enabling labor unions and employers of labor to provide at cost, protection against illness, injury and so forth, a co-operative in medicine for the use of industry seemed to be provided. Why should not that be done, as at the present time, by the regular insurance companies, who insure manufacturers against injuries and so forth to their employees.

Mr Spaulding stated that National Medical Care Plans was in no way intended to replace or to be workmen's compensation insurance. Employees were enrolled through their employers. The only thing that this national organization would be was an insurance company, set up under the laws of Illinois, where an employer and a union could equalize their benefits, all over the country. In some areas, the fee schedule was much lower than the present rate in New Hampshire. It was one of the principles of these national unions to provide benefits for all their members. The large employer groups were a result. The national organization, which could provide equalized benefits, would help to get subscribers back. The local operations would not be changed in any way. If the national level was set at \$100 for an appendectomy, and some plan only paid \$50 the local plan would still pay the \$50 and the national organization would pay the other \$50. It could never be a service contract, it would always have to be a contract of service only when the doctors agreed.

Dr Sycamore restated his motion that the House of Delegates approve the principle of a national service agency by associated medical plans.

This motion was duly seconded and was carried.

Dr Johnston moved that the House of Delegates formally ask the Blue Shield representatives in New Hampshire to look into the feasibility of setting up catastrophic illness insurance, and after they had looked at the actuarial tables and so forth, to report at a subsequent meeting.

This motion was duly seconded and was carried.

- (To be concluded)

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35471

PRESENTATION OF CASE

A fifty-three-year-old carpenter was admitted to the hospital because of intermittent jaundice.

The patient was perfectly well until approximately two and a half years before admission, at which time he had an illness characterized by marked weakness, malaise and jaundice, with no pain or fever. Recovery was complete in a four-week period. A second identical episode of jaundice occurred approximately two years before admission. He was studied at another hospital and a Graham test revealed a nonfunctioning gall bladder on repeated examination. He had a red-cell count of 3,000,000 and an icteric index of 60 units. The temperature chart was irregular, with occasional spikes to 102°F. The patient recovered in about three weeks. Several other attacks of painless jaundice with chills and fever occurred. Eight months before admission an elective cholecystectomy was performed at another hospital. The common duct was found to be much enlarged, it was opened and scooped out, but no stones were found. Large dilators were passed into the duodenum. The stomach and duodenum appeared normal. Cholecystectomy was performed, and the pathological report on the gall bladder was chronic cholecystitis. The patient did well postoperatively until six weeks before admission, when he had another episode of jaundice, ushered in by epigastric gaseous distress, marked anorexia and a 10-pound weight loss. The jaundice increased in severity, and the temperature spiked intermittently to 103°F. Because of the recurrence of jaundice, the patient was referred to this hospital.

On physical examination he was slightly emaciated and moderately jaundiced. The lungs were clear, and a Grade I apical systolic murmur was audible. The liver edge was felt 4 or 5 fingerbreadths below the costal margin and was nontender. The tip of the spleen was palpable. There was no ascites.

The temperature was 105.4°F, the pulse 100, and the respirations 24. The blood pressure was 140 systolic, 70 diastolic.

The urine was positive for bile, and the sediment contained several white cells and a rare granular cast. Blood studies disclosed a red-cell count of 2,100,000, with 8.5 gm of hemoglobin, and a white cell count of 45,800, with 91 per cent neutrophils. The total protein was 6.16 gm per 100 cc, with 2.72 gm of albumin and 3.44 gm of globulin. The nonprotein nitrogen was 30 mg per 100 cc, and the van den Bergh reaction was 3.4 mg per 100 cc direct and 4.6 mg indirect. The prothrombin time was 24 seconds (control, 17 seconds). The cephalin-flocculation test was ++ in twelve hours and ++++ in twenty-four hours. The alkaline phosphatase was 50.4 mg per 100 cc. The urine urobilinogen was 4.5 Ehrlich units. The stools were brown, and 1 out of 3 specimens examined gave a ++ guaiac reaction.

The patient had an almost daily elevation of temperature to between 102 and 104°F. Sulfadiazine had little effect. Several transfusions were given. On the twelfth hospital day, the patient went into shock and passed several bloody stools. Fluid and blood were given with some improvement. The jaundice became more marked. He died with a picture of pulmonary edema on the thirteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. LELAND S. MCKITTRICK*: I have not even the comfort today that goes with seeing the x-ray films, from which one constantly anticipates but rarely gets a great deal of help. There are certain things that seem to be perfectly clear cut. Here is a man, who for over two and a half years had recurrent attacks of epigastric pain, with dark urine, jaundice, sometimes clay-colored stools, chills and fever. I would not know how to make any diagnosis on a basis of the history except that this man had a cholangitis.

Now the real difficulties begin. We know that he was operated on eight months before entry, and that he had no stones, at least no stones were found, that he had a dilated common duct (the record does not say whether the duct was thickened, and it does not give any information about what was in the duct or information of the character of the bile or other important items that would be helpful), and that he had a large, dilated ampulla. That information is a little bit difficult to put together with complete satisfaction, because almost all the cases of cholangitis that I see have as a basis for the cholangitis a mechanical obstruction to the duct. In contrast here one finds a widely open ampulla with nothing in the duct. Nevertheless, I am forced, for want of any other explanation in the history, to say that this patient had had re-

*Visiting surgeon, Massachusetts General Hospital.

current attacks of cholangitis. Our major problem then is to try to determine what the background of that cholangitis was.

I suspect we have every right to believe that early in his career he had little or no liver damage. I do not know how much a negative biopsy of the liver means, but it must mean a good deal. After he came in here the condition was somewhat different. He had a large prostate for two and a half years. He then had a reversal of the albumin-globulin ratio and a prolonged prothrombin time. We do not know whether these were due to liver damage or something else because we do not know how long after entry he developed them. He apparently improved promptly after the use of vitamin K. Nevertheless, at the time of admission, there was reversal of the albumin-globulin ratio, a positive cephalin-flocculation test and possibly a prolonged prothrombin time. I think there is no question that he had liver disease, biliary in type and secondary to this process, that had been going on for two and a half years. The large spleen I would think to be quite in keeping with the longstanding recurrent episodes of infection.

I assume that this patient, who went into shock, passed several bloody stools and then died regardless of treatment, might well be considered to have died primarily of hemorrhage. Were it not for the underlying disease, blood loss alone would perhaps not have killed him, but it seems to me that the condition that finally caused his death was probably a fairly massive hemorrhage of some type. If he had an increase in his prothrombin time, it is perfectly possible for him to have had a massive hemorrhage from a diffuse process along the gastrointestinal tract. There, again, I do not know how one can possibly do more than guess where this hemorrhage came from—from an erosion or localized area or from a diffuse process. If we knew the subsequent prothrombin time, and if it had responded satisfactorily to vitamin K, which I am sure he was given, we would be less apt to expect a diffuse source of the bleeding as a cause for the hemorrhage, because the prothrombin time was not too prolonged. I am simply going to go on the assumption that in all probability this hemorrhage, which played a part in his death, came from a localized area rather than a diffuse area along the gastrointestinal tract such as we see in the late stages of jaundice and other conditions that interfere with the clotting mechanism.

That brings us down, if our reasoning is logical, to the problem of explaining two things: his final hemorrhage on the basis of a localized lesion and his recurrent bouts of cholangitis. These bouts lasted six weeks—that is a long time for a bout of cholangitis to last—and then spontaneously cleared up, and he was perfectly all right for a period of several months. I am going to go on the assumption that this man did have intermittent

blockage of the common duct. I just do not know how to explain it on any other basis. Intermittent blockage comes most commonly from a stone, but it could come from some type of growth. We know that carcinoma of the ampulla, or carcinoma of the head of the pancreas, may cause intermittent jaundice, but the thing that bothers me here about making either of those diagnoses is that this does not seem to have been a progressive lesion so far as the obstruction to the common duct is concerned. It was progressive so far as the evidence of cholangitis is concerned, and he died in my judgment ultimately of that combination. I cannot quite visualize the usual carcinoma of the ampulla or duodenum in that area as giving this kind of clinical picture. I would expect it ultimately to have become a more or less progressive, obstructive process, so I have to satisfy myself by laying aside the diagnosis of carcinoma of the ampulla of Vater or carcinoma of the duodenum or pancreas for something that is more intermittent. I know that I am not a good enough surgeon to find a stone in the common duct always, and we know the fact that a stone was not found does not mean that it was not there. A stone that has eroded into a vessel and causes ulceration, hemorrhage and death is a perfectly conceivable explanation for this condition. On the other hand he had clay-colored stools only occasionally. Some of these attacks lasted for six weeks, and it is difficult for me to believe that throughout this period he had a stone there, and particularly if it produced a block, that it did so for two to six weeks.

The other possibility is some kind of tumor, either benign or relatively benign, or so situated that it would intermittently block the common duct, causing essentially the same thing that a stone would cause. It would have been much more difficult to discover at operation. It may have become necrotic, with ulceration and bleeding as a final episode. It is conceivable that the patient had a polypoid tumor in the distal portion of the common duct that caused this type of picture. Because I want to be a little different, and not just bet on the horse that usually wins, it seems to me that some mechanism such as that would come nearer to satisfying my concept of this picture than that of stone. I simply am going to hazard a guess, and it is a guess, that he had some such obstruction as a polypoid tumor in the distal common duct that caused intermittent blockage, with superimposed cholangitis. I suspect that he had multiple abscesses of the liver at the time of death, and I believe that the precipitating factor in his death was probably hemorrhage from a localized area of necrosis and ulceration. I think also that he had a biliary type of cirrhosis.

DR SEDGWICK MEAD: Would you consider the possibility of liver abscess as precipitating the terminal event?

DR McKITTRICK Multiple, not single I would not know how to fit a single abscess into this picture

DR CHESTER JONES One of the things lacking in his picture was a spiking temperature I think we all considered the lack of a daily swinging temperature and chills very strong evidence against multiple liver abscesses

DR McKITTRICK Yes, I would agree

DR JONES It is always very pleasant to see someone else go through the same amount of sweating that one has gone through when confronted with a case like this Dr Myles Baker and I saw this patient over a period of three weeks before we and the house staff arrived at a final conclusion We thought that the cholangitis, jaundice, fever and laboratory data were in favor of obstruction and that there was a diffuse liver process resulting from years of intermittent partial obstruction In spite of that the liver biopsy was reported as normal I entertained the diagnosis of cirrhosis, doubting the correctness of the biopsy report, and asked to see the slide, it was sent to us from the other hospital I went over it subsequently with Dr Mallory It did not seem to fulfill the usual criteria that I would expect to find with biliary cirrhosis The section I saw, as I recall it, had among other things definitely dilated sinusoids They were very wide, and I wondered at the time and made a note that this might be Chiari's syndrome with blockage of hepatic veins Then the question came up concerning what might produce that condition Chiari's syndrome, especially one of hepatic-vein blockage, can be due to various abnormalities, the commonest of which is cancer It may be due to an inflammatory process It may be found in straight cirrhosis, not of the biliary type The terminal event, the massive hemorrhage, would make me wonder whether there was an active ulcerative lesion that was connected with the original cause of the disease I would think it would probably be placed in or near the ampulla of Vater, probably in the duodenum We were trying to get him ready for surgery of course

CLINICAL DIAGNOSES

Gastrointestinal hemorrhage
Cholangitis
Obstructive biliary cirrhosis

DR McKITTRICK'S DIAGNOSES

Polypoid tumor of common duct with ulceration and hemorrhage
Cholangitis
Biliary cirrhosis
Multiple abscesses of liver?

ANATOMICAL DIAGNOSES

Adenocarcinoma of ampulla of Vater
Hemorrhage, massive, into biliary and intestinal tracts

Cholangitis, acute and chronic, slight
Pancreatitis, chronic
Operative wound, old cholecystectomy

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY At post-mortem examination the intestinal tract and the common bile duct were filled with fresh, red blood On clearing that away we found the common duct to be widely dilated, as were the ampulla and the opening into the duodenum Around the area where the ampulla should have been was a large ulcer with a border of obviously carcinomatous tissue The primary lesion in this case was undoubtedly a tumor of the ampulla, and as Dr McKittick



FIGURE 1

stated, polypoid in the early stage but later becoming frank, ulcerative carcinoma It was a well differentiated and slowly growing adenocarcinoma (Fig 1) and could well have been present for two and a half years The liver was much enlarged, weighing 3000 gm The microscopical sections were characteristic of biliary cirrhosis I was surprised in view of the history that there was relatively little

evidence of cholangitis. The other findings were coincidental. There were no esophageal varices. The spleen was considerably enlarged, it looked like an infectious spleen rather than that of a portal hypertension. Nothing else of significance was found.

DR JONES: I assume that the original biopsy was taken close to the gall-bladder bed. How much difference is there between a biopsy from that location and a biopsy of the liver taken from a site farther away from the gall-bladder bed, in a patient with biliary cirrhosis?

DR MALLORY: In cases of frank cholecystitis there may be localized inflammation in the adjacent portions of the liver. It is not a fair picture of the liver as a whole. I do not think there would be any danger of missing a generalized process such as biliary cirrhosis from the taking of a biopsy. The danger is the reverse. One might discover a local lesion and interpret it as a general one.

DR MCKITTRICK: What do you suppose caused the episodes of obstruction? Edema with ulceration?

It is intriguing that the surgeon who operated found dilatation of the ampulla as you found at autopsy, and yet the patient still had these definite bouts of obstructive jaundice. There must have been obstruction to cause such a dilatation.

DR JONES: That original finding was eight months before.

DR MALLORY: Dr Kernohan, you have probably seen many cases of this type at the Mayo Clinic. Do you want to tell us about them?

DR JAMES W. KERNOHAN: I have seen this phenomenon several times: ulceration around the ampulla of Vater with intermittent jaundice, and at autopsy a papilla or common duct widely open, with terminal hemorrhage.

CASE 35472

PRESENTATION OF CASE

First admission. A sixty-two-year-old Italian housewife, para V, gravida VIII, was admitted to the hospital complaining of vaginal bleeding.

She had been well until the age of fifty, twelve years before admission, when her menstrual bleeding became very profuse. She was given "radium to the uterus" at another hospital, following which her periods ceased. Three weeks before admission a slight, constant, bloody, vaginal discharge began.

Physical examination showed an obese well developed woman in no discomfort whose only significant abnormality was an orange-shaped mass in the left lower quadrant. Urine and blood examinations were not remarkable. Vaginal smears were consistent with adenocarcinoma. Intravenous pyelogram, a barium enema and a metastatic series were negative. At operation a nodular tumor was found in the left cornu of the uterus and a radical

total hysterectomy with bilateral salpingo-oophorectomy was performed. Pathological examination showed an adenocarcinoma of the fundus, Grade III. Following an uneventful recovery the patient was discharged to the tumor clinic, where she received 3950 r from the million-volt machine with good response.

Second admission (fifteen months later). For the year following discharge she was seen at regular intervals. No sign of recurrence was noted, and the patient felt well and gained 15 pounds. Two months before her second admission she had a two-day episode of dull pain in the right lower quadrant unassociated with other symptoms and relieved by a hot water bottle. She was then well until six days before admission, when similar right-sided pain recurred, unaccompanied by gastrointestinal or urinary symptoms. No light stools or dark urine was noted. She consulted her physician, who, after finding one degree of elevation of temperature, advised hospitalization although the pain abated spontaneously.

Physical examination revealed a patient in no apparent distress. The temperature was 99.5°F. There was no abdominal spasm or costovertebral-angle tenderness. However an 8-cm, movable, slightly tender right-lower-quadrant mass was felt. The urine was normal. The hemoglobin was 12.0 gm per 100 cc, and the white-cell count was 8400. Intravenous and retrograde pyelograms showed displacement of the lower pole of the right kidney anteriorly. A barium enema disclosed incomplete filling of the cecum and confirmed the presence of an abdominal mass.

The patient was started on Crysticillin therapy in spite of which the temperature fluctuated between 99 and 102°F, although the white-cell count remained normal. On the ninth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR GORDON A. DONALDSON*: One would gather that this patient was the cause of considerable thought and study on the surgical service, where she remained nine days preoperatively. Inasmuch as the x-ray films were of such value, I think we ought to see them early to direct our discussion. I think it is of interest and of value that x-ray films taken fifteen months previously were reported as normal.

DR JOSEPH HANELIN: I have only the films of the present admission. The first examination done was a plain film of the abdomen, which was followed by an intravenous pyelogram, and later a retrograde pyelogram. On the intravenous pyelogram it is possible to see the large mass opposite the right iliac crest, extending almost an equal distance above and below the crest.

DR DONALDSON: Is that the cecum?

*Assistant surgeon, Massachusetts General Hospital.

DR HANELIN I am not certain. In a number of the films, although they are not described in the protocol, are two small calcifications in the region of this density. One is triangular in shape, and one is circular. The left kidney appears quite normal. The right kidney is unusually placed. The lower pole is swung medially and somewhat in an anterior direction. The ureter may be displaced slightly in a medial direction. The apparent displacement of the upper calyces probably results from the distortion caused by rotation of the kidney rather than an intrinsic renal lesion. Films of the chest and skull were normal. A barium enema done between the intravenous pyelogram and the retrograde study shows deformity of the cecum. The cecum is elevated, and in a spot film it is seen to terminate abruptly. The appearance of the cecal deformity is suggestive more of an extrinsic mass with a nodular outline than of a tumor arising from the cecum itself. In the spot films the two small calcium densities are again noted. They seem to be in relation to the edge of the deformed cecum and make one wonder about the possibility that they are fecaliths in the appendix.

DR DONALDSON I gather that the cecum does lie high. Also, this mass is larger than the protocol led me to believe, certainly larger than 8 cm. If this is a mass it is 20 by 20 cm, perhaps.

Two events took place in the interval between the time when the x-ray studies were read as normal and the present x-ray films. One is the finding of a definite adenocarcinoma of the uterus, which was removed. Moreover, this adenocarcinoma was a palpable one preoperatively. Because of the fact that it was palpable and she was given x-ray treatment after removal of it I would conclude that her cancer was an extensive one. I think the opinion in the gynecologic service is that x-ray treatment rarely need be given after radical total hysterectomy for fundal cancer unless gross disease such as peritoneal implants is left behind. There is one other point in favor of recurrent disease, and that is the site of the mass seen by x-ray study. It is possible to have recurrence in this location from carcinoma of the uterus because of the distribution of the ovarian lymphatics. They run up in this direction, and tumor or cells, after reaching the lymph nodes, could displace the lower pole of the kidney anteriorly. However, in spite of these points in favor of recurrent cancer, I should turn

to the other events that took place in the interim—that is, the onset of definite attacks of right-lower quadrant pain eight weeks before, lasting a couple of days, the other having occurred one week before and lasting approximately six days. These episodes were definite and caused the patient to go to a doctor.

This brings us to the latter part of the history and leaves us with a story of pain, the finding of this mass on physical examination and the x-ray report. I think it boils down to analyzing these points to bring us to a diagnosis.

In one last attempt to tie the present mass up with the previous operation, I wonder if this might have been a residual hematoma, or a foreign body resulting from previous operation. About a year ago at these conferences a case was presented* in which a hysterectomy had been done, with the subsequent development of a mass requiring reoperation approximately six or eight months later. At that time a large cyst was found—a persistent, slowly organizing hematoma around the left ovarian pedicle. In today's case, however, a mass had never been felt on numerous occasions in the Out Patient Department follow-up study, and I doubt if such a cyst was present. Another possibility is that this was secondary to the heavy x-ray therapy. Could it be that this was ileitis with abscess formation in a woman who was otherwise well and had gained 15 pounds in weight? I believe both are unlikely. I think Dr. Hanelin would agree that this tumor causes extrinsic pressure on the cecum and not within the cecum itself. We have to look outside the cecum. A huge lipoma at the pole of the cecum could give such a picture. The cecum and hepatic flexure are favorite sites for large-bowel lipomas. The mass is quite large, however.

Of course the obvious organ in this region is the appendix. Could this have been a carcinoid of the appendix? Finally, could it have been an inflammatory process in the appendix itself? The temperature did not respond to Crysticillin therapy. We do not know how much Crysticillin she received, but it is a fact that organized pus produced by the flora in the colon does not respond to antibiotics, and one usually has to resort to surgical drainage of such collections of pus. I think that is a point that directs us toward an abscess produced by the

*Case Records of the Massachusetts General Hospital (Case 35032)
Am. J. Med. 240:111-113, 1949

colon bacillus and other cocci. The most likely cause for such an abscess is the appendix. The white-cell count was not elevated. Very often in retrocecal appendicitis, in elderly people particularly, the white-cell count is not elevated. There are other points in favor of a retrocecal location. The x-ray picture showed displacement of the cecum anteriorly. The pain, moreover, began in the right lower quadrant and gave quite bizarre subjective symptoms. This is the story very often found in retrocecal appendicitis. I think it is very unlikely that the kidney was behind all this trouble. I am left with a diagnosis of inflammation, probably arising in the appendix, and in all probability well walled off by the cecum and omentum.

DR JACOB LERMAN: Did the retrocecal mass extend high enough to distort the kidney?

DR HANELIN: I would think not.

DR DONALDSON: Appendicitis going on for two months might be associated with large lymph nodes in that region, which possibly might distort the kidney.

CLINICAL DIAGNOSIS

Appendiceal abscess

DR DONALDSON'S DIAGNOSIS

Appendiceal abscess

ANATOMICAL DIAGNOSIS

Metastatic adenocarcinoma of appendix with appendiceal abscess

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: The surgical service's preoperative diagnosis was also appendiceal

abscess. At operation the surgeon disclosed a large, firm retrocecal mass that looked like an old appendiceal abscess. It was very adherent to the ileum and cecum but was freed from them without entering either organ. In the process what was believed to be the stump of the appendix was removed. When we received the material it was in several pieces. One piece, obviously the tip of the appendix, about 5 cm in length, was surrounded with brawny inflammation. The proximal piece was apparently opened and it was also part of the appendix. On microscopical examination the tip and distal parts of the appendix looked just like an appendiceal abscess. There were acute and chronic inflammation and fibrosis around and invading the wall of the appendix, which was very edematous, but the part adherent to the cecum, the proximal part that had broken off, contained in the serosa an area of adenocarcinoma, very similar to the carcinoma of the uterus previously removed. The appendiceal abscess about which there was no doubt, had therefore been produced by carcinomatous obstruction of the proximal portion of the appendix. There were some foci of calcification in one of the sections.

DR HANELIN: Was there any explanation for the apparent renal displacement?

DR CASTLEMAN: The surgeon did not mention it. I am sorry he is not here. In going over the old sections of the cancer of the fundus, it was apparent that the tumor was highly malignant, it had invaded the myometrium at the time of the first operation, and the ovaries and tubes were adherent to it.

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REJECTED SUITOR

OSCAR R. EWING, federal security administrator, appears to have misjudged the quality of his listeners in a speech made before the National Association of Retail Druggists on September 20. Mr. Ewing, apparently unmindful of the professional quality of the pharmacists' services, based his appeal for their support of compulsory health insurance almost entirely on the profit motive.

"Certainly," he reminded them at one point in his address, "any major progress we make in this age-old struggle against sickness and disease is sooner or later reflected in larger receipts for your own cash register." Again, in referring to the check-ups given last year to nearly two million children by public-health doctors or private physicians, he added, "And I don't doubt that most of the mothers wound up in the local drugstore with a doctor's prescription of one sort or another to be filled." And again, "Let me point out that the drug

trade flourishes in the shadow of the hospital," and "If we can double the number of hospital beds available — as we intend to do over the next ten years — the effect upon your business will be literally enormous." Nor are these the only examples of the theme song of this particular oration.

Since the days when the apothecary was often the doctor and the doctor usually compounded his own prescriptions, up to the present, when the large-scale pharmaceutical manufacturer is a close ally in the progress of modern medicine, the reputable druggist has been an unselfish partner of the reputable physician in the care of the sick. Working long hours, frequently holding himself available day and night for emergency service, the responsible druggist rightly considers himself as something much more than a tradesman.

Subsequent to Mr. Ewing's speech a resolution was passed by the Association repudiating the federal political health scheme.

Mr. Ewing, in his administration of the Federal Security Agency, has demonstrated his capacity for becoming a valuable and highly regarded public servant. There is little doubt that he is one of the able men of the present administration. The question can be raised, however, whether he is serving his country to his fullest capacity while he is almost obsessively preoccupied with the promotion of a plan to which the country is apparently not receptive.

PRIVATE SUPPORT OF SCIENTIFIC RESEARCH

IN THESE days of ever-expanding federal aid to, and participation in, scientific endeavor it is encouraging to consider the record of projects in scientific research that function entirely through contributions from private sources. Private philanthropy, in recent years, has received less than its due share of recognition, mainly owing to the fact that Government aid has been extended on such a scale and with such publicity that more modest contributions, by contrast, appear to be of small moment.

The achievements of investigators supported by grants from such sources as the Rockefeller and Carnegie foundations speak for themselves — even

when compared with work performed under the sponsorship of the federal Government. An example of the organizations that offer substantial, if little-publicized, aid to scientific research on a world-wide scale is provided by the Ella Sachs Plotz Foundation for the Advancement of Science. Of particular interest are the grants, made during the twenty-fifth year of the Foundation's existence, to men working on various experiments in the United States: to Dr. Charles P. Laman, of Harvard Medical School, for the purchase of apparatus essential to the continuation of metabolic studies in hibernation, to Dr. Bernard J. Miller, of Jefferson Medical College of Philadelphia to defray the cost of equipment for the direct determination of blood volume by measurement of the dye T-1824 in the circulation of the ear, to Dr. Carl Neuberg, of New York University, for research on inorganic and organic phosphates, to Dr. C. I. Reed, of the University of Illinois, for the purchase of x-ray apparatus for the study of metabolism of bone as influenced by various sex hormones, and to Dr. Ernst A. Scharrer, of the University of Colorado, for the purchase of amphibia for continuation of work on neurosecretion.

All due publicity should be given the aid offered by the Ella Sachs Plotz Foundation as well as the larger grants made in the names of the Markles, the Carnegies and the Rockefellers. This is not to deny that, at present and probably for years to come, federal support of scientific investigation will still be essential. But these sources of private aid should be kept in mind when the record of Government sponsorship is held up as evidence that extended federal participation and other steps along the road to state control of scientific research should be provided for. So long as the philanthropic organizations, great and small, continue their contribution no state dole in the sciences appears necessary.

IS SYPHILIS VANISHING?

UNDER the title of "The Vanishing Lesion," Dr. C. Morton Smith,¹ twenty-nine years ago, wrote the following sentences:

The disappearing of cutaneous syphilis lesions confronts us with a new problem. The teacher of clinical syphilis

must regard this changing condition with real apprehension. One no longer sees in the clinic the array of active lesions that were formerly available for teaching purposes.

Today, the evidence points not only to the further vanishing of cutaneous lesions but also to an actual decrease in the incidence of syphilis itself. This decrease is shown most strikingly in a table, published in a recent number of the *Journal of Venereal Disease Information*,² that indicates the sharp decline in latent and early cases of acquired syphilis reported by states and territories since the year 1941 when reporting by stage was first initiated by the various states.

Over a similar period the statistics of the Army and the Navy have shown decreases in the discovery rate of syphilis. Of course the discovery rate may not be the incidence rate, but the United States Public Health Service believes that an analysis of the accumulated figures gives support to the fact that syphilis is decreasing. Theoretically, more cases should have been detected if they existed because during the last few years contact investigation has improved, the medium of public appeal has been emphasized and one may assume that the effectiveness of case finding has improved rather than diminished.

It is possible that the widespread use of penicillin in the treatment of gonorrhea and other diseases accounts to some extent for the decreased incidence of syphilis. It had been thought that the amount of penicillin used for gonorrhea would be insufficient to control syphilis as well, but the follow-up study of men discharged from the armed forces after treatment of gonorrhea by penicillin has not, thus far, revealed any significant amount of syphilis that was masked by the drug. Such cases, however, should still be followed for the possibility of syphilis.

It is also possible, with the shorter schedule of therapy in use today, that the treatment of syphilis has been shifting from public clinics to the offices of private physicians. Whether the private physician reports cases of syphilis as faithfully as the clinics do is a matter of doubt, but available evidence indicates that the decrease reported in private practice is comparable to that in the clinics.

There are still many areas in the country in which well organized case-finding programs and reporting

systems have not yet been developed. Every effort should be made to extend the use of adequate case finding and reporting to the whole nation, and to detect all possible cases of syphilis that arise so that adequate treatment can be given and the late effects of the disease prevented.

Although the day of the "one-shot cure" for syphilis has not yet arrived and it is still too early to be sure that a latent period is not produced by penicillin therapy, it is encouraging that the incidence of syphilis has shown this definite decrease in the last few years.

REFERENCES

- 1 Smith C M. Vanishing lesion: new problem in teaching. *Arch Dermat & Syph* 2:639-648, 1920
- 2 Federal Security Agency. Cases of acquired syphilis reported by states and territories, fiscal year quarters 1941 to date. *J Ven Dis Inform* 30:209, 1949

THE CHRISTMAS SEAL

THE annual sale of Christmas Seals, between November 21 and December 25, not only serves as a reminder that the money contributed in this campaign provides the entire financial support of the National Tuberculosis Association and its 3000 affiliated organizations but also re-emphasizes the challenge offered by a disease that ranks seventh among the leading causes of death. Each year the Association asks for contributions so that its effort toward control and eventual suppression of tuberculosis may continue.

The facts about this disease are sobering, in spite of the progress that has been made. Tuberculosis kills nearly 1000 Americans a week — at a rate of 1 person every eleven minutes — and remains the leading cause of death among persons from fifteen to thirty-four years of age. It causes more deaths than any other infectious disease or any disease due to a germ, being responsible for 1 out of every 30 deaths among white people and 1 out of every 12 among Negroes. The economic losses are also serious: the care of tuberculous patients in hospitals in a single state (New York) cost \$23,000,000 last year, and expenditures from public and private sources in the country as a whole are estimated at

more than \$350,000,000 a year, to this figure must be added the cost of hospital construction, lost wages, lowered production and broken homes. The toll is even more disheartening when it is realized that, although the disease is both preventable and curable, at least 500,000 Americans have active tuberculosis, and only half these cases are known to health authorities.

It is this quarter of a million people on whom the program of control must be concentrated. Thus far, the most important step in this direction has been the chest x-ray examination, by means of which the disease can be discovered in its early, symptomless stage, when it is easiest to cure. Part of the activity of the tuberculosis organizations consists in group and, in co-operation with public health agencies, community-wide x-ray surveys. The year-round campaign of the National Tuberculosis Association and its subsidiary groups emphasizes education and dissemination of correct information, case finding, rehabilitation and medical research — a sound program of preventive medicine.

Tuberculosis, in the forty-five years of the Association's existence, has dropped from first to seventh place among the leading causes of death, the death rate being cut 85 per cent. This encouraging trend must be continued. But until control has reached the point where the disease no longer kills and no longer causes economic loss on a vast scale, the effort toward eradication must be supported. All physicians are urged to contribute generously through the purchase of Christmas Seals, the symbols of an excellent program of preventive medicine made possible by a voluntary and united response to the appeal of the sick and unfortunate.

Boston Eye and Ear Infirmary — *The new edifice in Charles Street, is nearly ready for the reception of patients. It is to us a complete architectural abortion. There is neither elegance nor convenience discoverable to our eyes, in its exterior. A beautiful site for a public building has, we think, actually been spoiled.*

Boston M & S J, November 21, 1849

MASSACHUSETTS MEDICAL SOCIETY



DIRECTORY OF OFFICERS AND FELLOWS

The 1949 edition of the *Directory of Officers and Fellows of the Massachusetts Medical Society* is now available. Fellows may receive a copy of the directory by writing to the Secretary at the Society Headquarters at 8 Fenway, Boston

H QUIMBY GALLUPE, *Secretary*

PHYSICIANS MUST TAKE OATH

To the Fellows of the Massachusetts Medical Society

The following memorandum from the Division of Vocational Rehabilitation of the Massachusetts Department of Education dated October 28, 1949, is of interest to any physician who may be employed by the Commonwealth

H QUIMBY GALLUPE, *Secretary*

To Rehabilitation Division Personnel
From Mr Edward D Callahan

Subject Chapter 619, Acts of 1949, "An Act barring certain people from the public service"

The above-mentioned act becomes effective on October 28, 1949. A copy is attached to this memorandum. The Attorney General has advised the Secretary of State that "It is my opinion that every person upon entering the employment of the Commonwealth or of any political subdivision thereof, including counties, cities, towns and districts, is required under the express terms of the statute, before entering upon the discharge of his or her duties, to take the prescribed oath, or affirmation, in the form set out in the statute and subscribe his or her name to it on a blank form prepared for the purpose, under the penalties of perjury. Under the terms of St. 1949, Chapter 619, it will not be necessary for anyone to take the oath or affirmation before a justice of the peace, or other officers qualified to administer oaths."

Under present interpretation of the new law it will be necessary for the Division to secure the signature to the oath card of any individual whose services are to be used by the Division. This signature is to be secured before any authorization for service is to be sent to an individual and before any proposal for service is sent to Administrative Office. Physicians whose services are to be used for a general or specialist examination, tutors, or any other individual whose services are to be used should be advised of the requirements of the new law and signature secured. The signed card should be attached to the proposal sent from the District Office to the Administrative Office. No proposal for service by an individual will be approved unless a signed card is attached with the exception that if a person has signed a card which has been sent to the Administrative Office subsequent proposals will be accepted without an additional signed card. It will not be necessary to secure signed cards from agencies such as schools, hospitals, or companies authorized to furnish employment training. The act applies to the services secured from an individual. When signed cards are received at Administrative Office they will be sent later to the Secretary of State for filing. If an individual whom you plan to use for service to the Division does not wish to sign a

card the Division cannot authorize the service. District Supervisors should advise me of any such refusals.

A supply of oath cards is transmitted herewith. It is not necessary to keep a copy of signed card in District Office but I suggest a list be kept of individuals signing cards in order to know that a second card does not need to be secured.

When a proposal is sent to Administrative Office a statement can be typed on proposal "Oath card attached." This statement should carry a check mark to the right. If no card is needed because a signed card has earlier been sent a statement "Oath card previously submitted" should be typed and a check mark made to the right of the statement.

Chapter 619

AN ACT BARRING CERTAIN PEOPLE FROM THE PUBLIC SERVICE

Chapter 264 of the General Laws is hereby amended by adding at the end the three following sections — *Section 13* No person who is a member of the communist party, or is a member of or supports any organization which advocates the overthrow by force, violence or other illegal or unconstitutional methods, the government of the United States or of this commonwealth shall be employed in any capacity by the commonwealth or any political subdivision thereof.

Section 14 Every person entering the employ of the commonwealth or any political subdivision thereof, before entering upon the discharge of his duties, shall take and subscribe to, under the pains and penalty of perjury, the following oath or affirmation —

"I do solemnly swear (or affirm) that I will uphold and defend the Constitution of the United States of America and the Constitution of the Commonwealth of Massachusetts and that I will oppose the overthrow of the government of the United States of America or of this Commonwealth by force, violence or by any illegal or unconstitutional method."

Such oath or affirmation shall be filed by the subscriber, if he shall be employed by the state, with the secretary of the commonwealth, if an employee of a county, with the county commissioners, and if an employee of a city or town, with the city clerk or the town clerk, as the case may be.

Section 15 Violation of section thirteen or fourteen shall be punished by a fine of not more than ten thousand dollars or by imprisonment for not more than one year, or both.

Approved July 30, 1949

NOTE — The above is applicable to "every person entering the employ of the Commonwealth or any political subdivision" hereafter. In the case of new employees (entering) see to it that they file such oaths before the city clerk or town clerk who will, no doubt, furnish the blank forms.

DEATHS

AKIN — Moses Akin, M.D., of Ellenville, New York, died on July 11. He was in his sixty-second year.

Dr Akin received his degree from Tufts College Medical School in 1925. He was a nonresident member of the Massachusetts Medical Society.

His widow and a sister survive.

GRANDISON — Wilfred G. Grandison, M.D., of Charlestown, died on November 6. He was in his seventy-fourth year.

Dr Grandison received his degree from Tufts College Medical School in 1901. He was a former president of the Charlestown Medical Society and a fellow of the American Medical Association.

His widow, a son, two daughters, three sisters and two brothers survive.

HEPBURN — James J. Hepburn, M.D., of Norwood, died on October 26. He was in his sixty-seventh year.

Dr. Hepburn received his degree from Harvard Medical School in 1909. He was formerly surgeon-in-chief of Boston City Hospital and was professor of surgery, emeritus, at Tufts College Medical School. He was a member of the New England Surgical Society and a fellow of the American College of Surgeons and the American Medical Association.

His widow, three sons and two sisters survive.

RUEL — Joseph A. Ruel, M.D., of Haverhill, died on July 28. He was in his seventy-first year.

Dr. Ruel received his degree from Tufts College Medical School in 1911. He was a member of the staff of Hale Hospital.

His widow, a daughter and a granddaughter survive.

RUSHFORD — Edward A. Rushford, M.D., of Salem, died on October 25. He was in his sixty-seventh year.

Dr. Rushford received his degree from Tufts College Medical School in 1905. He was a fellow of the American Medical Association.

His widow, a son and two daughters survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

KING — Francis B. King, M.D., of Derry, died on July 10. He was in his forty-sixth year.

Dr. King received his degree from Tufts College Medical School in 1934. He was formerly medical referee for Rockingham County and was a member of the staff of Alexander-Eastman Hospital in East Derry.

His widow, a daughter, a son, his mother and a brother survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The December schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

ORTHOPEDIC CLINICS	DATE	CLINIC CONSULTANT
Lowell	December 2	Albert H. Brewster
Salem	December 5	Paul W. Hugenberger
Haverhill	December 7	William T. Green
Brockton	December 8	George W. Van Gorder
Greenfield	December 12	Charles L. Sturdevant
Gardner	December 13	Carter R. Rowe
Worcester	December 16	John W. O'Meara
Fall River	December 19	David S. Grice
Springfield	December 20	Garry deN. Hough, Jr.
Pittsfield	December 21	Frank A. Slowick
Hyannis	December 22	Paul L. Norton

RHEUMATIC FEVER CLINICS

	DATES
North Reading	December 6, 13, 20, 27
Fitchburg	December 7, 14, 21, 28

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

INSTITUTE FOR SPEECH CORRECTION

Under the will of a Springfield physician, the Institute for Speech Correction is now receiving the perpetual income from a substantial legacy. All income from this fund is awarded in the form of tuition scholarships to pay that portion of a

student's tuition which he himself is unable to finance. Full scholarships are awarded to many worthy students. Thus far there have been ample scholarships to provide for all who need them.

Scholarships are now available for stutterers, lispers, deaf persons and persons of any age who are handicapped with other speech and voice disorders, upon recommendation of their family physicians.

The Institute is a nonprofit, educational corporation. Several eminent physicians and educators serve without remuneration on its board of trustees.

CORRESPONDENCE

AMERICAN CANCER SOCIETY

To the Editor The editorial entitled "First Things First," which appeared in the October 13 issue of the *Journal*, makes a plea for a united fund-raising drive for all national health organizations to take the place of the separate campaigns of the March of Dimes, American Red Cross, American Cancer Society and so forth. The editorial states, "No more than two drives should be tolerated by the people in any one community." (This refers to one joint drive for local charities and another joint drive for the national organizations.) The American Cancer Society is convinced that any such joint drive would be harmful to the people of the country and, this summer, has made the following statement explaining why it believes as it does:

The American Cancer Society is much more than a charity. The most fundamental reason why anybody should give money to the American Cancer Society, or work for it as a volunteer, is not to help somebody else — but to contribute to the future security of his family and himself.

The most important and extensive work of the American Cancer Society concerns research and education. These activities benefit rich and poor without distinction.

The greatest single reason why the American Cancer Society cannot agree to attempt raising the funds it needs through the federated plan is that to do so is unfair to the giver, and would probably increase the number of cancer deaths forthwith. Here is why: the Society's fund-raising effort takes place during the month of April, which has been designated by Congress as Cancer Control Month. Volunteer workers for the Society use the occasion of calling on people to secure contributions also to instruct and educate the givers on what to do about cancer, how to detect it in its early stages. The April cancer drive is a huge educational effort as well as a big job of fund-raising. The education of people to "see your doctor in time," to "watch for cancer's danger signals" — with detailed descriptions of what these signals are — is undoubtedly the most effective single weapon available to the American Cancer Society for saving lives now. This is how people are saved from the ravages of cancer today.

Experience has shown it is vitally important to carry out the fund-raising and the educational efforts together. When a person gives his money to fight against cancer, he feels he has a stake in the whole thing. He becomes more vigilant about his family and himself. It would be a needlessly dangerous experiment to try to separate the educational and fund-raising efforts in the war against cancer. Of course, educational work is carried on by the Society at all times during the year but the great push is during the fund-raising drive — when the Society's more than one million volunteers take to the field.

To suspend this nationwide life saving crusade, and instead to be pipe-lined funds effortlessly and by remote control — through federated drives — is totally unthinkable to anyone who knows anything about the cancer problem.

CHARLES C. LUND, M.D., President

American Cancer Society
(Massachusetts Division), Inc.

CONTROL OF LIPOATROPHY

To the Editor I read with great interest the paper "Lipoatrophy Following the Injection of Insulin" by W. S. Collins and associates in the October 20 issue of the *Journal*. These authors suggested a method of control of insulin fat atrophy by a simple procedure of repeated insulin injections into the depressed areas. In the interest of diabetic patients I believe that this suggestion should be accompanied with a warning that very often these areas of atrophy become unresponsive to injection because of fibrosis, with concomitant lack of expansibility. This causes the necessity of increasing the pressure on the plunger of the syringe to force the insulin into the resistant tissues. Mishaps, such as spillage when the needle slips off the syringe, and even breakage of the syringe frequently occur. Moreover, the absorption time of the insulin from the atrophied area is uncertain. These factors occasionally increase the difficulties of good control in the able diabetic patient.

JAMES C. BRUDNO, M.D.

Quincy, Massachusetts

BOOK REVIEW

Das large Becken. Geburtshilfliche Studie über das Assimilationsbecken. By Prof. Dr. Heinz Kirchhoff, physician-in-chief of the Municipal Women's Clinic, Lübeck. 8°, cloth, 144 pp., with 111 illustrations. Stuttgart: Georg Thieme, 1949. Imported by Grune and Stratton, Incorporated, New York. \$6.00.

The studies on which this monograph is based were begun at Kiel and Leipzig before the war and were completed in 1947 at the Women's Clinic in Lübeck. The author describes as an anatomic and clinical entity a developmental disturbance, the assimilation pelvis, first noted nearly half a century ago by Breus and Kolisko, but not hitherto recognized as of obstetric importance.

The assimilation pelvis, of which Kirchhoff describes three principal types, arises from variations in the transitional vertebrae between the lumbar and sacral regions, and is characterized by the presence of six lumbar vertebrae, by sacralization of the last lumbar vertebra and usually by the existence of five pairs of anterior and posterior sacral foramina. The result produces what has been called the canal pelvis, which Kirchhoff terms the long pelvis, because the length of the birth canal is actually greater than the internal conjugate diameter—it is longer than it is deep, or broad anteroposteriorly. It is not the same as the flat rachitic pelvis, with which it may be combined.

The assimilation pelvis Kirchhoff has found by x-ray examination to be much commoner than is ordinarily supposed. He believes it to be a frequent cause of dystocia and prolonged labor because it interferes with the normal mechanics of labor by preventing the engagement and descent of the head. It therefore becomes an obstetric problem of profound importance, and its recognition before labor is essential and imperative.

The book has 111 illustrations by Ingrid Schaumburg, and a bibliography of forty titles.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Campbell's Operative Orthopedics. Editor, J. S. Speed, M.D., associate editor, Hugh Smith, M.D. In two volumes. 4°, cloth. Vol. I, 879 pp., with 573 illustrations. Vol. II, 849 pp., with 566 illustrations. St. Louis: C. V. Mosby Company, 1949. \$30.00.

This new edition of a standard treatise is the joint work of eleven specialists. The first edition was published in 1939 and reprinted in 1942. Dr. W. C. Campbell died in 1941. The text has been revised, and chapters on preoperative and postoperative care, peripheral-nerve injuries and amputations

have been added and new sections have been written on mold arthroplasty, ruptured intervertebral disks and on difficult and unusual nonunions. The illustrations also have been revised by the elimination of a third of the original drawings, which have been replaced by twice their number. The whole field of modern orthopedics has been covered, and the material is well arranged. Lists of selected references are appended to the various chapters, and there are author and subject indexes for each volume. The publishing is excellent. The set is recommended for all medical libraries and orthopedists and surgeons interested in surgery of the bones, joints, muscles and tendons.

The Pharmacologic Principles of Medical Practice. A textbook on pharmacology and therapeutics for medical students, physicians, and the members of the professions allied to medicine. By John C. Krantz, Jr., professor of pharmacology, School of Medicine, University of Maryland, and secretary of the general committee of revision of the *United States Pharmacopoeia*, and C. Jelleff Carr, associate professor of pharmacology, School of Medicine, University of Maryland, and auxiliary members of the revision committee of the *United States Pharmacopoeia*. 8°, cloth, 980 pp., with 94 illustrations. Baltimore: Williams and Wilkins Company, 1949. \$10.00.

This new textbook is intended for the medical student and the practicing physician. The main portion of the text is arranged according to the systems of the body. The first part is devoted to history, principles and an introduction to drugs. The second discusses the antiseptic drugs, including the antibiotics. An appendix concerns the discovery and evaluation of new drugs. Lists of selected references are appended to the various chapters. A comprehensive index concludes the volume. The text on twenty-three subjects was referred to competent authorities for review and criticism before the final manuscript was prepared. The book, therefore, in a way is a composite effort of a number of specialists. The material is well arranged, and the publishing is excellent in every way. It is recommended for all medical libraries and to all persons interested in clinical pharmacology, and should merit a wide distribution.

Atlas of Neuropathology. By Wm. Blackwood, M.B., F.R.C.S.E., assistant pathologist, the National Hospital, Queen Square, London, T. C. Dodds, F.I.M.L.T., F.I.B.P., F.R.P.S., laboratory supervisor, Department of Pathology, University of Edinburgh, and lecturer to the Society of Radiographers (Fellowship Course) Scottish Branch, and J. C. Sommerville, A.I.M.L.T., senior technician, Department of Neuropathology, University of Edinburgh and Scottish Mental Hospitals' Laboratory. With a foreword by Professor A. Murray Drennan, M.D., F.R.C.P.E., F.R.S.E., professor of pathology, University of Edinburgh. 8°, cloth, 199 pp., with 262 illustrations. Baltimore: Williams and Wilkins Company, 1949. \$9.00.

This atlas presents in one small volume a large number of illustrations in monochrome and color of the pathologic conditions most often met with in neuropathology. The illustrations have been made from slides and specimens, and the volume is intended for clinicians and pathologists beginning the study of the subject. The work is based on the demonstrations given in the laboratory of the Scottish mental hospitals and in the University of Edinburgh over a period of years. The material is divided into ten parts, the first of which illustrates the various cells and the reaction of the neurone to disease. The succeeding parts portray vascular disease, organismal infection, demyelinating disease of unknown etiology, intoxications and deficiencies, degenerations, mechanical trauma, hydrocephalus and displacements, tumors and errors in development. The text is confined to descriptions of the conditions illustrated. There is a good index. The plates are excellent, and the printing, which was done in Great Britain, is very good. The atlas should be in the reference collections of the large medical libraries and available to neurologists and pathologists.

The Epidemiology of Hemolytic Streptococcus during World War II in the United States Navy. By Alvin F. Coburn, M.D., The Rheumatic Fever Research Institute, Northwestern University Medical School, and Donald C. Young, M.D., medical director, Communicable Disease Service, Herman

Kiefer Hospital 8°, cloth, 229 pp., with illustrations and tables. Baltimore: Williams and Wilkins Company, 1949 \$4.00

This monograph constitutes a study of streptococcal diseases as they occurred in the four years of World War II, among more than 3,000,000 young Americans. It is a comprehensive study and supplies quantitative data on contamination by hemolytic streptococcus. There is a bibliography of seventy-three titles and a good index. The volume is well published. It is the type of book that should be in all medical libraries.

Early Recognition of Disease. Edited by Sir Heneage Ogilvie, K.B.E., D.M., M.Ch., F.R.C.S., and William A.R. Thomas, M.D. 8°, cloth, 134 pp. London: Eyre and Spottiswoode Publishers, Ltd., 1949. 10s. 6d. net. (*The Practitioner Handbooks*).

This monograph forms one of the English *Practitioner Handbooks*. It is a composite work by a group of fourteen specialists and covers the field of internal medicine, the eye, orthopedics, arthritis, cancer, mental disorders, neurologic diseases, complications of pregnancy and pediatrics. It is intended as a ready guide for the general practitioner. There is a good index and the small volume is well published.

Some Common Psychosomatic Manifestations. By J. Barrie Murray, M.A., M.D. (Cantab.), M.R.C.P., diagnostic physician, Tavistock Clinic, honorary physician, Bolingbroke Hospital, and honorary physician, The Margaret Street Hospital for Diseases of the Chest, London. 12°, paper, 101 pp. London: Oxford University Press, 1949. \$2.50.

In this small book the author discusses the effort syndrome and its symptoms, physical signs and differential diagnosis. There are also short chapters on the "low-back syndrome" and on treatment of psychosomatic disorders. There is a short bibliography and an index. The book is well published.

Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Sixth revision of the International Lists of Diseases and Causes of Death. Adopted 1948. Volume I. 8°, paper, 376 pp. Geneva, Switzerland: World Health Organization, 1948.

This sixth edition of a standard classification succeeds the *International Lists of Causes of Death*, the title of the fifth edition. It differs appreciably in its scope and arrangements from previous editions. It provides a single list applicable to both morbidity and mortality statistics, it defines the content of the individual categories of the classification with as much international uniformity as possible, considering the differences in languages and terminology, it represents for the first time international agreement on a uniform method of selecting the main cause to be tabulated, if more than one cause is stated on the death certificate, and the manual includes international rules to assist the compiler of morbidity and mortality statistics in the application of the classification. In the introduction the history of attempts to classify diseases from the time of Sauvages (1706-1777) to the present is given. The manual is well published and should be in all medical libraries.

NOTICES

ANNOUNCEMENTS

Dr. John J. Byrne announces the opening of an office at 520 Commonwealth Avenue, Boston, for the practice of surgery.

Dr. John A. Conroy announces the removal of his office to 684 Commonwealth Avenue, Newton Centre.

Dr. Ward I. Gregg announces the removal of his office to 1269 Beacon Street, Brookline.

WOMAN'S AUXILIARY TO SUFFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Woman's Auxiliary to Suffolk District Medical Society will be held in Sprague Hall, Boston Medical Library, 8 Fenway, Boston, on Thursday, December 1, at 2:30 p.m. The speaker will be Mrs. Charles E. Ayers, of Worcester, president of the Woman's Auxiliary to the Massachusetts Medical Society.

LECTURES ON MORALS AND MEDICAL CARE

The last two of a series of four lectures on morals and medical care, sponsored by the Workers of the Common Life, will be delivered by Joseph F. Fletcher at St. John's Church, Roxbury Crossing, at 8 p.m., on the following dates:

Tuesday, November 29: The Right to Control Parenthood.
Tuesday, December 6: The Right to Die.

Admission is free.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be held at the Peter Bent Brigham Hospital, Boston, on Monday, December 5, at 8:15 p.m., Dr. Samuel A. Levine presiding.

PROGRAM

Some Electrocardiographic Observations in Potassium Intoxication. Drs. Harold D. Levine, John P. Merrill, Walter Somerville and Stephen Smith, III.
Heart-Muscle Metabolism in Cardiac Failure Studied by Coronary Venous Catheterization in Man. Drs. Walter T. Goodale, Robert E. Olson, Donald B. Hackel and Lewis Dexter and Miss Florence W. Haynes.
Circulatory Dynamics in Constrictive Pericarditis. Dr. C. Glenn Sawyer, Richard Gorlin, James W. Dow, Eugene C. Eppinger and C. Sidney Burwell.
Salt Excretion during Water Diuresis. Dr. William B. Schwartz.
Further Observations on the Surgical Treatment of Coarctation of the Aorta. Dr. Robert E. Gross.
Paroxysmal Ventricular Tachycardia. A study of 107 cases. Drs. Samuel A. Levine and Charles A. Armbrust, Jr.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, December 7.

11:00 a.m. - 12:00 p.m. Clinical Session by Dr. Charles A. Janeway and staff. Amphitheater, Peter Bent Brigham Hospital.
12:00 p.m. - 1:00 p.m. Clinicopathological Conference. Amphitheater, Peter Bent Brigham Hospital.
2:30 - 4:30 p.m. Scientific papers dealing with ACTH. Amphitheater of Building C, Harvard Medical School.
4:45 p.m. Open discussion by members of the Massachusetts Chapter of the American Academy of Pediatrics concerning the findings of the recently published Academy study. (Members of the society are cordially invited).
5:30 p.m. Refreshments at Longwood Towers.
6:30 p.m. Dinner at Longwood Towers (price, \$3.25).
7:30 p.m. Psychiatric Aspects of Rheumatic Disease. Dr. Alfred O. Ludwig.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3-MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

NOVEMBER 29. Lecture on Morals and Medical Care. Notice above.

NOVEMBER 30. New England Conferences on Allergy and Related Subjects. Page 798, issue of November 17.

DECEMBER 1. Woman's Auxiliary to Suffolk District Medical Society. Notice above.

DECEMBER 1 AND 2. American Institute of Architects. Page 630, issue of October 20.

DECEMBER 2. The Present Investigation of Cortisone and ACTH. Dr. Chester S. Kiefer. Boston Dispensary Clinical Staff. Audiology. Joseph H. Pratt. Diagnostic Hospital.

DECEMBER 3-8. American Academy of Dermatology and Syphilology. Page 762, issue of November 10.

DECEMBER 5. New England Cardiovascular Society. Notice above.

DECEMBER 5-10. Symposium on Inhalational Therapy. Page 47, issue of October 20.

DECEMBER 6. Lecture on Morals and Medical Care. Notice above.

DECEMBER 7. New England Pediatric Society. Notice above.

DECEMBER 8. Evaluation of the Treatments of Arthritis. Dr. Walter Buer, Pentucket Association of Physicians. 8:30 p.m., Haverhill.

DECEMBER 13. New England Society of Anesthesiologists. Page 77, issue of November 17.

DECEMBER 15. 94th Infantry Division Lecture. Page 798, issue of November 17.

DECEMBER 28 AND 29. American Association for the Advancement of Science. Page 350, issue of September 1.

(Notices concluded on page xviii)

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THROMBOANGIITIS OBLITERANS*

An Evaluation of Therapy, with Special Reference to Lumbar Sympathectomy

EDWARD HAMLIN, JR., M D † RICHARD WARREN, M D, ‡ AND HARRISON E. KENNARD, M D §

BOSTON

THROMBOANGIITIS obliterans is an uncommon disease. The diagnosis was made at the Massachusetts General Hospital in only 180 cases during the twenty-year period 1926-1945. It makes up for its infrequency, however, by its chronicity, the 180 patients having had a total of 780 different admissions, or an average of over 4 admissions per patient, each one of which averaged thirty-two days or a grand total of 24,960 patient days or sixty-eight-and-one-third patient years. Thus, the problem of therapy is of considerable importance both to the patient and on general economic grounds.

The diagnosis of thromboangitis obliterans at the Massachusetts General Hospital is made for the most part on clinical evaluation. Surgical specimens have shown to a large extent the non-specific histology of the inactive phase of the disease. At the Massachusetts General Hospital a young male with evidence of obliteration of the major arteries in the lower extremities without x-ray evidence of calcification and almost always with a relatively long history of intermittent claudication fulfills the necessary criteria for diagnosis. A history of migrating phlebitis, ulceration of toes, increased susceptibility to cold and excessive use of tobacco serve as confirmatory evidence.

The sufferer from thromboangitis obliterans is relatively young, well under the age when arteriosclerosis may produce much the same clinical picture. Eighty-seven per cent of our patients were in the third to fifth decades, and 41 per cent were between thirty and forty years of age (Table 1).

It should be noted that 22 patients are listed in Table 1 as having thromboangitis obliterans although their first admission to this hospital occurred at fifty years of age or older. We believe that

by the time the age of fifty is reached thromboangitis obliterans will seldom initiate symptoms and also that in an old case symptoms at the age of fifty may be attributed to superimposed arteriosclerosis and yet in this group, the evidence on review of the records favors the diagnosis of thromboangitis obliterans, although, as emphasized above, it is by no means conclusive.

Incidentally, one of these more elderly patients was one of the 2 women in our series, aged sixty-

TABLE 1 *Ages, by Decades, of Patients at Time of First Admission*

AGE	NO OF PATIENTS	PERCENTAGE
10-19	1	less than 1
20-29	26	14
30-39	75	41
40-49	58	32
50-59	18	10
60-69	4	2
Total	180	

one, and the diagnosis was established by histologic examination.

It has been mentioned above that the symptoms of intermittent claudication in thromboangitis obliterans are usually of long duration. In this series the average interval between onset of symptoms and admission to the hospital was fifty months.

From a geographic standpoint 57 per cent of our patients were born in this country, 34 per cent in Russia or Poland, 6 per cent in Canada and 4 per cent each in Italy and Portugal. It is of interest that only 21 per cent were of Jewish extraction.

No particular occupation was engaged in by the group, there being an even spread among nine listed types of work. This is in agreement with the findings of others.¹

Since smoking is considered a contributory cause of the failure of therapy and by some, of the disease

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itself, we have endeavored to determine its incidence. Of 155 of the 180 patients from whom we could obtain definite information, 108 smoked more than 20 cigarettes a day, 44 smoked less than a package, and only 3 claimed that they never smoked.

TREATMENT

Almost all the forms of therapy that have been advocated for thromboangitis obliterans have been employed by the Vascular Service of the Massachusetts General Hospital at some time. These include nonspecific foreign protein, intravenous administration of hypertonic saline solution and of ether, histamine, ascorbic acid and sodium citrate solution. Some of these therapies were employed on only a very few patients, but none have impressed the Vascular Service sufficiently to ensure their continued use at the Massachusetts General Hospital.

Supportive

At the present time, the treatment of legs without open lesions consists of "foot hygiene," postural exercises² as modified by Allen,³ sympathectomy⁴ and an attempt at education of the patient including interdiction of tobacco.

Each patient is given a printed sheet, which contains information concerning the care of the feet and toenails and also diagrams and instructions including specific timing for postural exercises. The timing is determined by observation of the period necessary to produce blanching of the feet on elevation and full engorgement on dependency. It is believed that these times should be redetermined at intervals of a month or so.

Properly performed exercises are regarded as advantageous to the patient in two ways: there is good reason to believe, on the basis of repeated observations, that the development of collateral circulation is aided, and there is a benefit to morale, because the patient realizes that he is actively engaged in the therapy of his own disease.

It has been found that the patient's interpretation of the exercises must be checked at every opportunity, otherwise, gross errors and probably no benefits result.

Many of the forms of therapy described above could be included under "general education," but a specific effort is made to inform the patient of the nature of his disease, what the prognosis is, how it may be bettered, what sort of occupation he may engage in, how pain and discomfort may be handled and, most important of all, the need for avoidance of tobacco.

Obviously, the individual patient should be viewed with a proper perspective. It is better to enjoy life without legs than to spend every waking hour doing exercises to save legs that can never be of further use. Possibly, it is better in rare cases for a patient to smoke and thereby endanger his

legs than to suffer severe withdrawal symptoms, but if the patient disregards his instructions it should be because he has calculated the risk rather than through ignorance.

Sympathectomy

Lumbar sympathectomy has been considered to be the most effective form of therapy that we have employed. Since 1936 virtually all patients with thromboangitis obliterans have had bilateral lumbar sympathectomies. This involves 85 patients.

Since the etiology is unknown and the nature of the pathologic process is not entirely clear, it is impossible to think of sympathectomy as a specific therapy. Indeed it is almost certain that remissions and exacerbation of the disease still continue unaltered, but that the symptoms are usually ameliorated. The release of vasoconstrictor impulses can affect only the undiseased collateral circulation. It is apparent, therefore, that the earlier in the course of the disease sympathectomy is performed, the more benefit should be derived. Whether sympathectomized and hitherto undiseased arteries and arterioles are protected to any extent from the encroachment of thromboangitis obliterans is a question that at the moment cannot be answered.

Results. A follow-up study has been made in the hope of shedding light on two important questions—namely, the influence of sympathectomy on preservation of the extremity and its effect on the relief of symptoms.

Of the 170 legs that have been sympathectomized, 23, or 13.5 per cent, were subsequently amputated. If cases in which amputation was performed less than three months after sympathectomy are excluded (and since in many of these cases sympathectomy was performed as a last resort it seems reasonable to exclude them), the amputation rate is lowered to 9.4 per cent. These figures are to be compared with the 67 (35.2 per cent) of the total 190 legs not subjected to sympathectomy that were amputated. The figures are not, of course, strictly comparable since the unsympathectomized groups to a large extent were treated early in the twenty-year period, before some of the more modern concepts of general therapy were evolved, and also because there has been a longer period in which further arterial obliteration might develop. Nevertheless, it appears probable that some legs have been preserved by sympathectomy.

In an attempt to evaluate the symptomatic relief following lumbar sympathectomy, it was obvious that evaluation, difficult enough in any case, had better be confined to a definite symptom such as pain. We turned our attention, therefore, to patients with intermittent claudication or steady pain in their extremities unassociated with an open ulcer at the time sympathectomy was done. This strict requirement gave us only a small group of 30 extremities belonging to 18 patients that we

carefully studied. The patients were personally interviewed and examined.

The results are summarized in Table 2, which shows that although only 60 per cent of the extremities that could be evaluated showed improvement in intermittent claudication, 86.6 per cent demon-

TABLE 2 *Results One Year or More after Lumbar Sympathectomy in 24 Patients*

RESULT	GENERAL DISCOMFORT	INTERMITTENT CLAUDICATION
	NO OF CASES	NO OF CASES
Patient cured	2	3
Patient greatly improved	18	4
Patient improved	6	8
Patient unimproved	2	6
Patient worse	2	4
Total limbs evaluated	30	25

strated improvement in general comfort—that is, increased warmth, disappearance of numbness and so forth.

Some⁵ have believed that sympathectomy should be more efficacious in patients with less damage to the circulation as evidenced by palpable popliteal pulsations. Table 3 shows that we have not found this to be true. The good and poor results are about evenly distributed among the patients with and without palpable popliteal pulses.

The optimum extent of lumbar sympathectomy has always been debated. The debate has centered around whether the first lumbar ganglion should be removed along with the second and third or whether removal of the latter two alone is sufficient. Although evaluation of this point can never be finally made until postoperative testing of the sympathetic denervation is accurately done, we have some information derived from the operator's impression of the extent of the sympathectomy performed. Table 4 correlates the removal or non-

TABLE 3 *Correlation of Presence or Absence of Popliteal Pulse with Improvement in Intermittent Claudication (25 Extremities)*

STATUS OF INTERMITTENT CLAUDICATION	STATUS OF POPLITEAL PULSE AT TIME OF SYMPATHECTOMY	
	PRESENT	ABSENT
Cured		3
Greatly improved	3	1
Improved	4	4
Unimproved	2	4
Worse	2	2
Totals	11	14

removal of the first lumbar ganglion with the effect on intermittent claudication. Although the numbers are too small to be conclusive, there is no tendency for them to suggest that the additional removal of the first lumbar ganglion contributed markedly to the subjective result.

The danger of interfering with sexual function is always debated when the extent of lumbar sympathectomy is considered for patients in this age group. We were able to analyze the results on 16 patients who had had unilateral (5) or bilateral (11) lumbar sympathectomy. We found that none of the 5 patients who had had a unilateral lumbar sympathectomy of any degree (4 of our 5 included the first lumbar ganglion) had any trouble with potency or ejaculation. Of the bilateral lumbar sympathectomies the first lumbar ganglion was removed bilaterally in 6 patients, all of whom had some trouble with sexual function (3 with ejaculation, and 3 with potency). In 1 of these patients the trouble with ejaculation was only temporary, lasting for three months. In another, ejaculation was not abolished but decreased by 75 per cent. In the other 4 cases trouble was complete and permanent. Two of the patients with bilateral lumbar sympathectomies had the first lumbar ganglion removed on one side but not on the other. Both had complete and permanent loss of ejacula-

TABLE 4 *Correlation of Removal or Nonremoval of the First Lumbar Ganglion with Effect in Intermittent Claudication (25 Extremities)*

EFFECT ON INTERMITTENT CLAUDICATION	FIRST LUMBAR GANGLION REMOVED	FIRST LUMBAR GANGLION NOT REMOVED
	NO OF CASES	NO OF CASES
Cured	—	3
Greatly improved	1	3
Improved	7	1
Unimproved	4	2
Worse	2	—
Totals	14	9

tory power. In 2 patients only of the bilateral group were the first lumbar ganglions spared on both sides. Neither of these showed any interference with sexual function. Poppen and Lemmon⁶ found that 39 per cent of males who had the first and second lumbar ganglion removed from above on both sides for arterial hypertension had trouble with sexual function. They postulated that lower lumbar ganglions often participate in the regulation of such function. From this point of view, therefore, as well as from that of the clinical result, it is concluded that it is rarely advisable or necessary to remove the first lumbar ganglion when a lumbar sympathectomy for thromboangiitis obliterans is performed in young men. It is also important, if a bilateral operation is to be performed, to warn the patient of possible trouble, since owing to the variable arrangement of ganglions in this region,⁷ it is not always possible to preserve the first lumbar ganglion.

Since only 5 of the 18 patients could be said to have definitely abstained since the diagnosis was first made, the effect of smoking on this group of

patients could not be accurately assessed. Of the 7 extremities in these 5 patients, 6 were improved in varying degrees, only 1 was unimproved. We are of the opinion, from talking to the patients who did not abstain, that there is a great individual variation in sensitivity to smoking in patients with thromboangitis obliterans. Separation of the sensitive from the nonsensitive persons can be made, however, only by a process of trial and error that, at best, is unsatisfactory. Furthermore, it is well known that even those who are most sensitive will often continue to smoke in the face of the threatened loss of a limb. We therefore consider that a strict edict should be issued to all patients with thromboangitis obliterans that they abstain from smoking for life.

It is important that the surgeon have some knowledge of when maximal improvement may be expected to follow sympathectomy. In 13 of the 16 patients who were improved after lumbar sympathectomy, the maximal improvement was immediately established in 6. In 3 the improvement was complete within two months. By the end of a year the remaining 4 had experienced all the improvement that they obtained.

Amputation

Ninety legs were amputated in 64 patients (26 patients had bilateral amputations). This is an incidence of 25 per cent legs lost. Many of these operations were performed soon after the patient was first seen at the hospital and so do not represent a failure of therapy, however, the incidence is high.

Of the amputations done above the level of the metatarsals, 18 were done at the point of election in the lower leg. Twenty-seven were low-thigh and the remainder or 45 were Gritti-Stokes amputations. Because of the relative youth in this group and the fact that in thromboangitis obliterans arterial obliteration tends to be more peripheral and the collateral circulation better than in arteriosclerotic gangrene, the Gritti-Stokes amputation is usually to be preferred over the more conservative low-thigh amputation. It gives a weight-bearing stump that is relatively easy to fit with a prosthesis and allow maximum activity.

However, it is probable that with modern therapies such as sympathectomy and chemotherapy more lower-leg amputations should be performed than we have thought permissible in the past.

Minor amputations. Minimal gangrene is frequently best treated by amputation of one or more toes. In our series 47 patients, or 26 per cent, had amputations that averaged three and three-tenths toes apiece.

Toe amputations should never be done until the level of gangrene has been clearly established and it appears probable that the resulting wound will heal. Crushing of the appropriate peripheral nerves as described by Smithwick⁸ continues to prove a

useful form of therapy. It is of great value in certain patients with painful open lesions when the sensory denervation may allow adequate daily dressings and the sympathetic denervation some additional beneficial release of vasoconstrictor impulses. At present, transmetatarsal amputation, as recommended by McKittick⁹ in diabetic patients, is considered as an alternative to multiple toe amputations. We have performed a few highly successful ones in patients seen since this series was concluded.

Although thromboangitis obliterans may be a generalized arterial disease, only 10 of our patients, or 6 per cent, have required amputation of fingers. No amputation above the level of the finger was required in the upper extremity. In these 10 patients a total of 40 fingers were amputated. In two patients who had lost almost all their digits as well as both legs, the finger stumps still showed nicotine stains indicating that smoking is indeed most difficult to give up.

Seventeen upper extremities were sympathectomized. It is impossible to draw conclusions about the result of these operations except that the subjective impression was favorable.

DISCUSSION

In reviewing this series of patients with thromboangitis obliterans, we are impressed by the severity and chronicity of the disease. That our therapy has improved is manifest by the decrease in length of hospital stay. The group as a whole required thirty-two days for each admission. In 1945 the average admission had become reduced to nineteen days. The patient today is far more likely to be economically self-supporting than he was a decade ago. This we attribute mostly to comfort or lack of pain brought about by sympathectomy.

That more must be accomplished therapeutically is obvious, but it appears unlikely that great strides will be made until a better understanding of the nature and cause of the disease is arrived at.

SUMMARY

Experiences at the Massachusetts General Hospital in the treatment of 180 patients with thromboangitis obliterans in the twenty-year period 1926-1945 are described.

The natural course of the disease is reviewed, and useful therapeutic measures are outlined.

Although 35 per cent of 180 patients required one or more major amputations, lumbar sympathectomy early in the course of the disease has materially reduced the incidence of major amputations and has proved to be the most valuable method of therapy in our experience.

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PARENTERAL AND AEROSOL ADMINISTRATION OF ANTIHISTAMINIC AGENTS IN THE TREATMENT OF SEVERE BRONCHIAL ASTHMA*

HYMAN J RUBITSKY, M D,† ELLIOTT BRESNICK, M D,‡ LEON LEVINSON, M D,§
GEORGE RISMAN, PH D,¶ AND MAURICE S SEGAL, M D ||

BOSTON

IT IS a widely held opinion that bronchial asthma may be due to the liberation of free histamine from its usually bound state,¹⁻⁴ although many conflicting observations make this view far from universal. The oral administration of "antihistaminic" drugs (blocking agents) has proved of limited value in the management of bronchial asthma.⁵⁻⁷ Recent observations by other investigators and the results of protection studies performed in our laboratory have suggested that the parenteral use of these drugs may be indicated in the treatment of severe bronchial asthma.

Feldberg⁸ and Szczygielski⁹ have shown that histamine is capable of causing the release of epinephrine from the adrenal medulla. Staub¹⁰ and Farrerons-Co¹¹ have demonstrated essentially the reverse of this phenomenon — namely, that the intravenous injection of epinephrine or sympathin produces a marked increase in plasma histamine. This reciprocal relation has been termed the "histamine-sympathin see-saw." The epinephrine-fast state in intractable asthma may be a disruption of this "see-saw."¹²⁻¹⁴ In this condition large amounts of histamine are possibly present owing to allergic "shock,"¹⁵ anoxia¹⁶ and the further outpouring of histamine consequent upon continued epinephrine release from the patient's own adrenal medulla, and the repeated therapeutic administration of epinephrine. The "epinephrine-fast" patient may therefore present a situation similar to histamine being essentially unopposed. It is in this connection that the administration of specific antihistaminic agents would exhibit whatever value they may have in the clinical management of

asthma, by "balancing" the deranged histamine-sympathin "see-saw."

Yonkman and his associates¹⁷⁻¹⁹ described potentiation of the effects of epinephrine in the cat after the administration of tripeleennamine. This "adrenergic potentiation" was observed in both excitatory and inhibitory effector mechanisms. Similar potentiation of the vascular effects of epinephrine, after Antergan,²⁰ Benadryl^{21, 22} and Neo-antergan,^{23, 24} as well as tripeleennamine, has been reported by other observers. Experiments are in progress to determine whether antihistaminic agents have the ability to potentiate the protection afforded by sympathomimetic drugs, anticholinergic drugs and aminophylline against histamine-induced and methacholine-induced dyspnea and bronchospasm in patients with bronchial asthma.²⁵

Oral administration of antihistaminic agents may prove undependable. It has been shown that occasional patients, who demonstrated poor protection against histamine-induced dyspnea and bronchospasm when these drugs were administered orally, did show significant protection when the intravenous, rectal and aerosol routes were employed.²⁶ Taub²⁷ obtained clinical relief from various allergic phenomena following parenteral administration of antihistaminic agents after large oral doses of these drugs had proved ineffective. Rosenberg and Blumenthal²⁸ reported 4 cases of poison-ivy dermatitis in which immediate relief of pruritus followed intravenous injection of diphenhydramine. One subject was then placed on a maintenance dose of 50 mg orally every four hours and then 100 mg every two hours and experienced no relief. The authors concluded that "the only explanation felt plausible is that absorption from the gastrointestinal tract was impaired." Serafini,²⁹ McGavack³⁰ and Arbesman³¹ have also noted variable absorption rates of antihistaminic drugs from the gastrointestinal tract during the course of various studies.

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COMPARATIVE PROTECTION STUDIES EMPLOYING DIPHENHYDRAMINE AND TRIPLENNAMINE BY VARIOUS ROUTES

An analysis of Figure 1 and 2, in which are summarized the degree of protection afforded by oral, intravenous, rectal and aerosol administration of diphenhydramine and tripeleennamine against histamine-induced and methacholine-induced dyspnea and bronchospasm in asthmatic subjects reveals

are reached within fifteen to thirty minutes by the rectal route. Somewhat greater protection against methacholine-induced dyspnea and bronchospasm is obtained by these agents administered by the intravenous and rectal routes. The intensity and duration of significant antihistaminic protection conferred by the aerosol route (about two hours) is remarkable considering the minute dose employed. The technics used in the assembling of these data, by which controlled conditions not

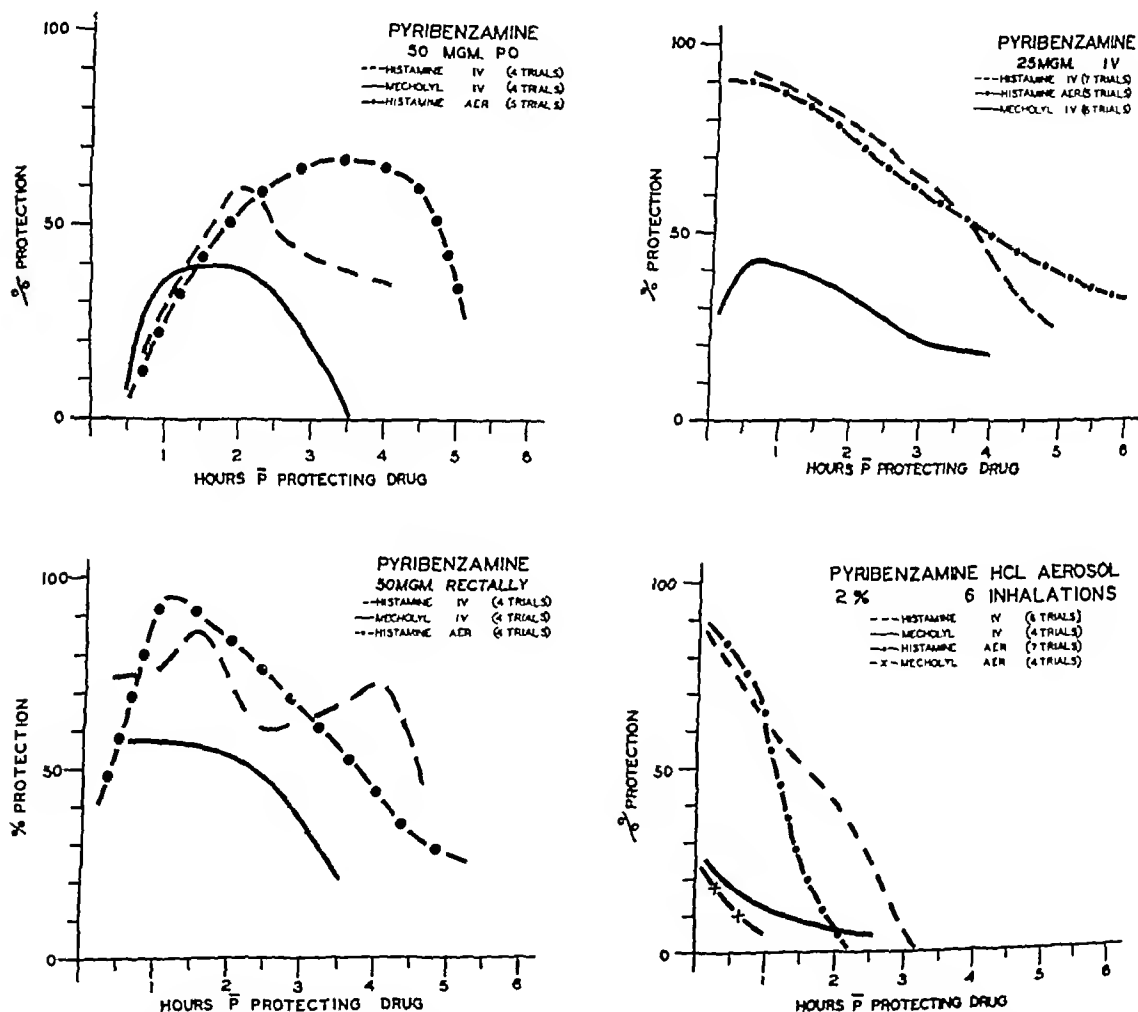


FIGURE 1 Protection Afforded by Oral, Intravenous, Rectal and Aerosol Administration of Tripeleennamine Hydrochloride (Pyribenzamine) against Dyspnea and Bronchospasm Induced by Histamine and Methacholine in Asthmatic Patients

the following significant features, which suggested the possible value of these agents in the management of the asthmatic patient

Significant protection (40 per cent) is not attained until sixty and ninety minutes with oral diphenhydramine and tripeleennamine, respectively. Immediate and almost complete antihistaminic protection is conferred by the intravenous and aerosol routes. High degrees of antihistaminic activity

usually present at the bedside can be achieved, have already been fully described.^{29, 33}

METHODS

We have used diphenhydramine* and tripeleennamine† in the treatment of 15 patients seriously ill with bronchial asthma. Doses ranged from 20

*Kindly supplied by G. D. Searle and Company, Chicago, Illinois.
†Kindly supplied by Ciba Pharmaceutical Company, Summit, New Jersey (Pyribenzamine).

to 50 mg of either agent and were administered intravenously at a rate not exceeding 10 mg per minute. To avoid chemical incompatibility, these drugs should not be mixed with solutions of aminophylline, if an infusion containing the latter drug is being administered, the antihistaminic agent may be injected into the rubber tubing close to the needle.

The most common side reactions observed in our patients were drowsiness and dizziness, par-

crease in the tenacity of the sputum were noticed several hours after the administration of tripele-namine, which McElin and Horton³¹ have also observed and which is possibly related to its anticholinergic properties.

Once having relieved the severe bronchospasm, we have successfully maintained many of our patients during convalescence with antihistaminic agents by the aerosol or rectal routes, or both, as supplements to other therapy. The aerosol route,

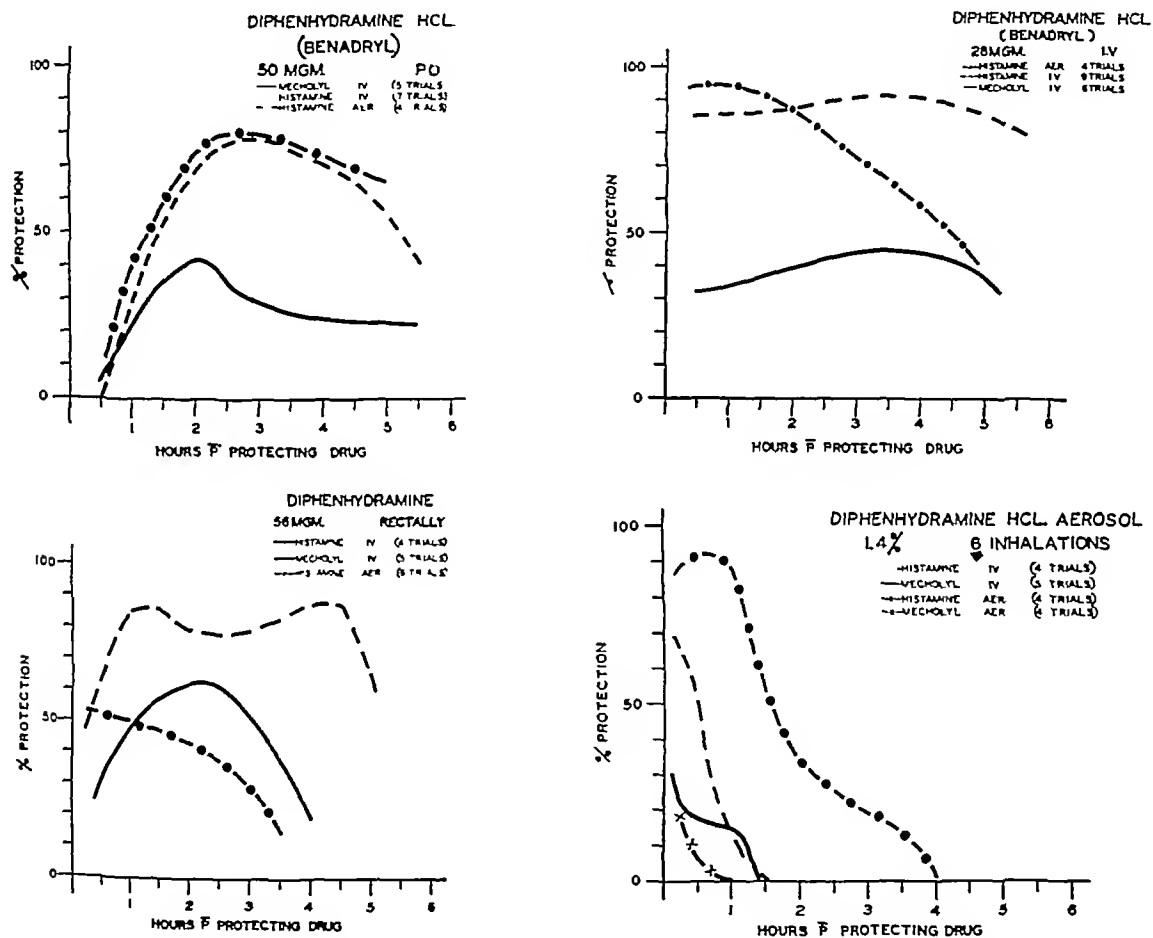


FIGURE 2 Protection Afforded by Oral, Intravenous, Rectal and Aerosol Administration of Diphenhydramine against Dyspnea and Bronchospasm Induced by Histamine and Methacholine in Asthmatic Patients

ticularly in the upright position, which usually disappeared gradually within one or two hours. Other less frequent effects noted in a total of 102 separate administrations of diphenhydramine were headache, transient chilliness, nausea, fatigue, palpitation, pallor, blurred vision, tachycardia and the "alert reaction." Essentially similar side reactions were encountered in 43 intravenous administrations of tripele-namine. In some cases a moderate diminution of expectoration and an in-

creasing a 2 or 5 per cent tripele-namine solution, either alone or mixed in equal parts with a bronchodilator, in a Vaponefrin nebulizer, has afforded gratifying relief. This is especially true when physical factors such as exposure to cold appear to play an important role. Rectal administration of tripele-namine or diphenhydramine (25 to 50 mg) has likewise been surprisingly efficacious over prolonged periods. For rectal instillation one may employ capsules of diphenhydramine, puncturing

the ends of the capsule before insertion into the rectum, or either drug may be given in solution, alone or in combination with aminophylline. Addition of diphenhydramine to solutions of aminophylline may result in the formation of a milky suspension, this reaction apparently does not interfere with the action of either drug given rectally.

The 15 patients in this series were selected after they had proved partially or completely refractory to either one or a combination of the following epinephrine subcutaneously, various bronchodilator aerosols, aminophylline intravenously or rectally, meperidine, helium-oxygen and "bronchial catharsis." Whenever possible, vital-capacity readings were taken in an attempt to obtain more objective evidence of improvement in pulmonary ventilation. Significant relief or restoration of epinephrine sensitivity was afforded in 10 cases.

CASE REPORTS

CASE 1 E S, a 26-year-old woman, had had eczema and perennial bronchial asthma all her life, necessitating eight previous hospitalizations. There was a history of familial allergy. She had had pneumonia at the age of 16. Decreases in her vital capacity of 1000 cc or more could regularly be induced during asthma-free periods by the intravenous injection of 0.01 to 0.02 mg of histamine. She had been maintained comfortably on bronchodilator aerosols for many months, many oral preparations and rectal administration of aminophylline had afforded no relief.

After an absence of 3 months, she returned to the clinic on September 10, 1948, with a history of increasingly severe bronchial asthma over the previous 4 days. She was greatly fatigued, somewhat tremulous and so dyspneic that it was impossible to obtain satisfactory vital-capacity determinations. She had been taking epinephrine subcutaneously every hour or so and bronchodilator aerosols even more frequently, with rapidly diminishing relief. Intravenous and rectal administration of aminophylline was likewise essentially ineffective and merely precipitated an "alert reaction." After six inhalations of Isuprel (1:200 solution) had proved ineffective, 25 mg of tripeleminamine was given intravenously. The dyspnea was greatly relieved after only 5 mg had been injected. By the time the total amount was given, she was no longer dyspneic, her vital capacity was 1800 cc. The only side effect noted was mild drowsiness. Ten minutes later, six inhalations of Isuprel 1:200 were again administered with an immediate rise of her vital capacity to 2200 cc, at which level it remained.

In the light of this patient's previous history, it is probable that were it not for the dramatic relief afforded by the intravenous injection of tripeleminamine, hospitalization would have been necessary. Although not so impressive as in the other cases reported, the restoration of sympathomimetic sensitivity resulting from the antihistaminic is nonetheless noteworthy.

CASE 2 M G, a 22-year-old single woman had had bronchial asthma for 11 years, at first seasonal but later perennial. Prior to being followed in our clinic, frequent hospital admissions had been necessary. She exhibited sensitivity to dust, mixed feathers and several foods, both clinically and by skin tests. When she was symptom free, predictable drops in her vital capacity of 1000 cc or more could be produced with 0.015 mg of histamine intravenously.

The effectiveness of intravenous antihistaminic therapy has been dramatically demonstrated in this patient on many occasions. On August 31, 1948, at the height of the ragweed-pollen season and during the course of a protection study in which histamine was being employed intravenously as the

bronchospastic agent, she experienced moderate asthma, lasting more than an hour. Her highest vital capacity was 2400 cc, whereas her usual control readings ranged from 3600 to 4000 cc. Isuprel inhalations were without effect. Tripeleminamine hydrochloride, 25 mg, was then administered by vein. Her vital capacity rose to the normal level (3500 cc) in 3 minutes, but dyspnea and falling vital capacity recurred, and the effects of tripeleminamine were no longer discernible 30 minutes later. Isuprel (1:200 solution, six inhalations) was given again at this time, with an increase in vital capacity to 4200 cc and relief lasting 80 minutes. Her asthma then recurred once more, and Isuprel (1:200 aerosol solution, nine inhalations) was ineffective. She was given 28 mg of diphenhydramine intravenously, diluted to 5 cc, with almost instantaneous relief after 1 cc had entered the vein. A vital capacity of 3400 cc was maintained for 30 minutes, and, as it began to drop, Isuprel (six inhalations) produced a further rise to 4000 cc. She remained at this level for 1 3/4 hours, and was discharged for the day, essentially asymptomatic. No side reactions from either drug were noted.

On September 9 the patient returned with severe bronchial asthma, which had been refractory to Isuprel aerosol, rectal administration of aminophylline, and epinephrine injected subcutaneously. She was perspiring profusely and extremely dyspneic, and was unable to blow up the vital-capacity apparatus. Diphenhydramine, 28 mg, was slowly administered intravenously. No sooner had the injection been begun than a profound relief again occurred and was objectively manifested by vital-capacity readings of 2000 cc within 5 minutes. Ten minutes after the diphenhydramine, Isuprel (1:200 solution, six inhalations) was given with even further relief. Her vital capacity rose to 3200 cc, at which level it persisted for 90 minutes. As before, no drowsiness or other effects were noted.

On November 12, after sudden changes in the weather, which had frequently precipitated asthmatic paroxysms in the past, she came to the clinic in severe bronchospasm that again was refractory to her usual therapy. She was given ten inhalations of an aerosol produced from a 1:4 per cent solution of diphenhydramine. Her vital capacity, which had been unobtainable, rose to 2800 cc, and after six inhalations of Isuprel 1:200 aerosol, it increased to 3200 cc, at which level it persisted for over 1 hour.

There is little doubt that parenteral antihistaminic therapy prevented not only hospitalization but also the progression of the asthma to the truly intractable state. Restoration of sensitivity to bronchodilator drugs with "adrenergic potentiation" was clearly and objectively demonstrated on the three occasions here reported and during several exacerbations since. It seems that diphenhydramine is the preferable drug in the patient, although no notable side effects occurred with either agent.

CASE 3 M K, a 55-year-old married woman, had suffered from bronchial asthma for 4 years. Until her present illness, the attacks had never been severe and had generally been relieved by epinephrine subcutaneously. Repeated skin tests were reported as negative. It was believed that emotional factors, as well as respiratory infections, contributed greatly to recurrences of the asthma. In April, 1948, a severe attack of asthma, which necessitated hospitalization, developed. On an extensive program of continuous aminophylline infusions (in 5 per cent glucose and water, meperidine and aerosols of a bronchodilator spray), she made a good recovery and was discharged within 10 days.

She then remained essentially well for 2 weeks, when she had a relapse and once again presented a picture of typical status asthmaticus. At this time she was entirely refractory to a continuous intravenous infusion of aminophylline, sympathomimetic amines by various routes, oxygen and numerous sedatives. She was then started on a program of intravenous injections of tripeleminamine, 50 mg every 4 hours. After the initial dose, bronchospasm became less marked, and the patient was considerably relaxed and somewhat drowsy. These injections were continued for the first 24 hours, and

*This case has previously been reported elsewhere.¹¹

the dose was gradually lowered to 40, 30, and 20 mg at intervals of approximately 1 day. The drug was entirely discontinued after 5 days of treatment.

Approximately 20 minutes after the initial intravenous dose of tripeleannamine she was given 0.3 mg of epinephrine subcutaneously. Subsequently, dyspnea and wheezing became still less marked. Furthermore, she did not complain of the troublesome palpitation and headache that epinephrine had produced previously. After the second injection of the antihistaminic agent, it was observed that she could once again return to aerosols of one of the sympathomimetic amines with considerable relief and without the side reactions previously observed. It was further noted that her tolerance for aminophylline returned under this program. She continued to make excellent progress, and after the 5th day, all intravenous therapy was discontinued and she was placed on a program of rectal administration of aminophylline and tripeleannamine and aerosols of one of the sympathomimetic amines. She has remained symptom free under this program.

These results are of particular interest because they demonstrate that restoration of epinephrine and aminophylline sensitivity can also be obtained in patients with "intrinsic" bronchial asthma with parenteral antihistaminic therapy. Several other favorable effects of this regimen that merit comment are the desirable sedative side reactions in such patients and the absence of the nausea and the "alert reaction" that aminophylline had previously produced.

CASE 4 J. S., a 24-year-old single unemployed veteran, had had hay fever and asthma for the past 2 years, occurring from May to the first frost. Prior to coming to the clinic, he had required injections of epinephrine and aminophylline every evening on the Accident Ward. With Hydrylin, Isuprel aerosol and rectal administration of aminophylline, he fared very well for 3 weeks during his usually worst season.

On September 7 he entered the clinic with severe bronchospasm. His vital capacity was 1600 cc., as compared with previous readings, which varied from 4600 to 5000 cc. Neither Isuprel aerosol nor rectal administration of aminophylline had helped. Epinephrine, 0.25 mg., was given subcutaneously. Only slight clinical improvement was noted with an increase in vital capacity to 2400 cc. 5 minutes later. His asthma recurred in a short time, however, and his vital capacity fell to 1300 cc. After the intravenous injection of 28 mg of diphenhydramine, marked relief was experienced with a rise in vital capacity to 3200 cc. Five minutes later, Isuprel (1:200 solution, six inhalations) effected a further increase of vital capacity to 3800 cc.; this state persisted for 45 minutes longer before he was sent home.

Here again, sensitivity to sympathomimetic agents following intravenous antihistaminic therapy was promptly restored. The patient experienced moderate drowsiness and drying of the pharynx and tracheobronchial tree, which subsided within two hours.

CASE 5 W. S., a 17-year-old boy, had had asthma for 15 years occurring concomitantly with hay fever from June to early August. He had been hospitalized three times with severe "epinephrine-fast" and "aminophylline-fast" asthma. Predictable bronchospasm could be produced with intravenous or aerosol administration of methacholine; the patient exhibited no change in vital capacity after 0.05 mg of histamine intravenously.

On September 6, 1948, he entered the clinic with moderately severe bronchospasm, his vital capacity being 1400 cc. (His usual readings varied from 4000 to 4900 cc.) Epinephrine, 0.25 mg subcutaneously, produced no clinical response, and 20 minutes later his reading was only 200 cc higher. Twenty-eight mg of diphenhydramine was administered intravenously, with no appreciable change in vital capacity, al-

though he did comment that his chest "felt lighter." When 0.25 mg of epinephrine was again injected 10 minutes later, almost complete relief of the dyspnea occurred, with a rise in vital capacity to 2400 cc., which persisted for 1 hour. He was then discharged, the slight drowsiness produced by the diphenhydramine having subsided.

In view of this patient's past history of resistance to epinephrine and aminophylline preceding his three previous hospital admissions, it seems that restoration of sensitivity to epinephrine avoided hospitalization and further distress. We have noted similar results from intravenous injection of diphenhydramine, particularly in elderly patients and patients who were relatively histamine-insensitive during protection studies, relief being forthcoming not so much from the antihistaminic per se as from the sympathomimetic agent after sensitivity had been restored.

CASE 6 I. C., a 24-year-old married woman, gave a history of seasonal bronchial asthma and hay fever of 6 years' duration. When first seen on the ward she was anxious, tense and moderately dyspneic after having received little or no objective relief from two injections of epinephrine and 0.5 gm of aminophylline given intravenously. Her vital capacity was 1300 cc. She was given 28 mg of diphenhydramine intravenously, with prompt relief of her dyspnea and a rise in her vital capacity to 2300 cc. Six inhalations of Isuprel (1:200 aerosol) 8 minutes later raised her vital capacity 500 cc. more, even though she was very drowsy at the time. Several minutes later she fell asleep. She experienced no further marked respiratory distress during the remainder of her hospital stay.

CASE 7 F. M., a 25-year-old married woman, had a 20-year history of seasonal asthma and hay fever, for which frequent hospital admissions had been required. In addition to eczema in childhood, there was a strong family history of allergy. Skin tests showed marked positive reactions to ragweed and dust. Predictable dyspnea was readily produced in the laboratory with 0.025 mg of histamine intravenously during her asthma-free intervals.

Although a regimen of oral administration of diphenhydramine and potassium iodide and Isuprel by inhalation kept her comfortable during the entire pollen season, she experienced moderately severe bronchospasm with the onset of the first cold weather, as she had done the year before, when hospitalization had been necessary. After 2 sleepless and distressing nights, during which Isuprel inhalation was required every 30 to 60 minutes and aminophylline suppositories (0.5 gm) were without appreciable relief, she came to the clinic. Her vital capacity was 700 cc. She was apprehensive, fatigued, tense and in severe respiratory distress. A marked nonproductive cough was present. Isuprel by inhalation was repeated but was again without effect. Diphenhydramine was administered intravenously, and after the injection of 2 cc. (approximately 10 mg) her dyspnea was greatly relieved. The only side effect noted was slight drowsiness. Ten minutes after diphenhydramine, her vital capacity was 1800 cc. Six inhalations of Isuprel (1:200 aerosol) further increased her vital capacity to 2400 cc.

Hospitalization was probably prevented in this patient by the prompt relief afforded by diphenhydramine and the restoration of sympathomimetic aerosol sensitivity it effected. She also noted, thereafter, that if she took an aerosol of equal parts of 5 per cent tripeleannamine and Isuprel (1:200 solution) prior to going out into the cold, the onset of an asthmatic paroxysm, which had been poorly controlled by bronchodilator aerosols alone, was prevented. The efficacy of the rectal

the ends of the capsule before insertion into the rectum, or either drug may be given in solution alone or in combination with aminophylline. Addition of diphenhydramine to solutions of aminophylline may result in the formation of a milky suspension, this reaction apparently does not interfere with the action of either drug given rectally.

The 15 patients in this series were selected after they had proved partially or completely refractory to either one or a combination of the following epinephrine subcutaneously, various bronchodilator aerosols, aminophylline intravenously or rectally, meperidine, helium-oxygen and "bronchial catharsis." Whenever possible, vital-capacity readings were taken in an attempt to obtain more objective evidence of improvement in pulmonary ventilation. Significant relief or restoration of epinephrine sensitivity was afforded in 10 cases.

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On November 12, after sudden changes in the weather, which had frequently precipitated asthmatic paroxysms in the past, she came to the clinic in severe bronchospasm that again was refractory to her usual therapy. She was given ten inhalations of an aerosol produced from a 14 per cent solution of diphenhydramine. Her vital capacity, which had been unobtainable, rose to 2800 cc, and after six inhalations of Isuprel 1:200 aerosol, it increased to 3200 cc, at which level it persisted for over 1 hour.

There is little doubt that parenteral antihistaminic therapy prevented not only hospitalization but also the progression of the asthma to the truly intractable state. Restoration of sensitivity to bronchodilator drugs with "adrenergic potentiation" was clearly and objectively demonstrated on the three occasions here reported and during several exacerbations since. It seems that diphenhydramine is the preferable drug in the patient, although no notable side effects occurred with either agent.

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She then remained essentially well for 2 weeks, when she had a relapse and once again presented a picture of typical status asthmaticus. At this time she was entirely refractory to a continuous intravenous infusion of aminophylline, sympathomimetic amines by various routes, oxygen and numerous sedatives. She was then started on a program of intravenous injections of tripeleennamine, 50 mg every 4 hours. After the initial dose, bronchospasm became less marked, and the patient was considerably relaxed and somewhat drowsy. These injections were continued for the first 24 hours, and

*This case has previously been reported elsewhere.¹¹

subsequent to the repeated use of epinephrine, suggested the possible value of these agents in the management of severe bronchial asthma.

Fifteen acutely ill asthmatic patients, 8 in the "intractable" state, were treated and maintained with intravenous, aerosol and rectal administration of diphenhydramine and tripeleminamine. The case histories of 7 patients are presented. Significant relief from bronchospasm or the prompt restoration of epinephrine sensitivity followed the intravenous administration of antihistaminic agents in 10 of the 15 patients.

The most favorable therapeutic results were obtained in patients who had previously been found to be "histamine sensitive" during protection studies. The poorest results occurred in patients with obstruction of the tracheobronchial tree by inspissated plugs of mucus, elderly patients with significant and irreversible cardiac and pulmonary disease and histamine-insensitive persons. Many of the patients in this series were satisfactorily maintained during remission with antihistaminic drugs both by the rectal route, alone or combined with aminophylline, and by the aerosol route, alone or combined with a bronchodilator.

Parenteral antihistaminics should be employed only as adjuncts to other effective therapy in the management of the patient acutely ill with bronchial asthma.

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instillation of the aminophylline-diphenhydramine combination was also impressive

DISCUSSION

In this series of 15 cases of acute bronchial asthma, the intravenous administration of diphenhydramine or tripeleennamine resulted in clinical improvement in 10. In some cases marked amelioration of dyspnea directly followed the administration of the antihistaminic agent. In others the effect of the drug was indirect, by enhancing the bronchodilator powers of subsequently administered sympathomimetic drugs ("adrenergic potentiation"). The sedative action ("hyoscine effect") of diphenhydramine especially was also of value.

Several authors have commented upon the efficacy of parenteral administration of antihistaminic agents in asthma. Rosenberg and Blumenthal²⁸ treated 3 patients with severe acute attacks of bronchial asthma, employing doses of 30 to 40 mg of diphenhydramine intravenously. Although in 2 cases there was no appreciable change, the third patient exhibited immediate objective relief. Cohen²⁵ controlled an attack with as little as 8 mg of diphenhydramine intravenously. However, Jenkins and his co-workers²⁶ obtained indifferent results from diphenhydramine given intravenously in 8 cases. It has been our experience, particularly in elderly patients with asthma, that when direct relief from the antihistaminic agent is not forthcoming, the restoration of adrenergic response that may follow is often therapeutically important.

It appears, however, that the effectiveness of therapy with these agents is possibly attributable to some other factor than their ability to antagonize histamine. McGavack^{27, 28} and others^{22, 29} have demonstrated the marked anticholinergic and anti-barium chloride action of diphenhydramine, which we have confirmed in asthmatic patients (Fig 1 and 2) both for this drug and, to a lesser degree, for tripeleennamine.²⁶ Inasmuch as many investigators believe that cholinergic mechanisms in the etiology of asthma and other allergic phenomena are at least as likely as histamine mechanisms,^{32, 40, 41} this property assumes considerable possible clinical significance.

Whereas the side effects produced by intravenous injection of antihistaminics are frequently undesirable in the ambulatory patient, drowsiness, relaxation and sleep may be highly desirable in the severely ill patient. Mild drowsiness is also noted after the rectal administration of either agent. We have not observed any significant cumulative effects with parenteral administration of antihistaminic agents. The diminution of expectoration and increase in the tenacity of the sputum that may be observed later have not been troublesome when effective expectorant therapy is also given.

We have found the combination of aminophylline with either diphenhydramine or tripeleennamine given rectally two or three times daily to be effective in maintaining many patients after cessation of severe asthma. We have also encountered favorable results in several patients with an aerosol, employing a 2 or 5 per cent tripeleennamine solution, or 1.4 per cent diphenhydramine solution, either alone or mixed with equal parts of solutions of sympathomimetic amines. The use of these combinations is particularly effective as a prophylactic measure in patients whose asthma is precipitated by exposure to cold. Feinberg⁶ and Arbesman⁷ have also noted relief with tripeleennamine aerosol in individual patients.

Parenteral antihistaminic therapy is by no means a panacea for the management of the severely ill asthmatic patient, and we have encountered patients in whom no relief was forthcoming from these agents. Waldbott and Young⁴² have even observed an aggravation of asthma after the use of antihistaminic agents. This therapy is presented only as an effective adjunct to other proved procedures in the management of the seriously ill patient, with particular emphasis on physiologically directed therapy and "bronchial catharsis."^{43, 44} Our poorest results have occurred in patients with obstruction of the tracheobronchial tree by inspissated plugs of mucus, elderly patients with significant and irreversible anatomic disease of heart or lungs and histamine-insensitive persons. The last observation was particularly striking in 2 young patients (B L and E C) in whom bronchospasm could be induced during clinically asthma-free intervals only by methacholine. Both developed severe bronchial asthma accompanying acute bronchitis and exposure to cold, and required hospitalization. No significant relief was afforded by parenteral administration of antihistaminic agents in either of these patients, even when large doses were given. Of interest in this regard are the observations by Fuchs et al,⁴⁵ who point out that in only 1 of the 23 per cent of their asthmatic patients helped by oral diphenhydramine was organic heart or lung disease present, whereas in the 77 per cent not receiving relief, organic heart or lung disease or an active sinus infection was present in all.

SUMMARY

The relative ineffectiveness of "antihistaminic" agents in severe bronchial asthma when given orally is well known. We have demonstrated prolonged and high degrees of protection against histamine-induced, and to a lesser extent against methacholine-induced, dyspnea and bronchospasm after the intravenous and rectal administration of "antihistaminic" agents in the laboratory. These observations and those of other investigators, indicating that large amounts of histamine may be released in allergic "shock" and hypoxia, and particularly

five minutes, + when the sulfur powder sank to the bottom immediately but floated in a dilution of the urine with water of 1:1, ++ when the sulfur sank also in the urine diluted 1:1, and +++ when the powder sank in higher dilutions.

Studies of the excretion of cholic acids in the urine of alcoholic patients had the following results: of 660 specimens of urine of 600 patients examined, + tests were found in 13.94 per cent and ++ to +++ tests in 5.46 per cent. That means that liver-cell damage was demonstrable with this test in 19.4 per cent. This number of positive tests is considerably less than the figures of 30.07 per

cent that in the more chronic stage of liver damage the cephalin-flocculation test was still positive while the urobilinogen test and the cholic acid test were negative. The biopsies revealed the severe damage to the liver cells and the fast improvement after modern treatment.

The last test used in these studies was the methylene blue test for bilirubin in the urine (Franke¹⁰). This procedure is considered as very useful by a great number of investigators, though it is not specific for bilirubin. The technic of Gellis and Stokes¹¹ was followed. The test was rated as + when blue color appeared with 5 drops, when 6

TABLE 1 *Results of Liver-Function Tests in an Alcoholic Patient**

DATE	UROBILINOGEN	CHOLIC ACIDS	CEPHALIN FLOCCULATION at 48 hr	SERUM BILIRUBIN		REMARKS
				DIRECT mg/100 cc	INDIRECT mg/100 cc	
Nov. 14	+++ (1:650)	+++				
Nov. 15	+++ (1:540)	+++	+++	2.8	3.2	Direct diazo reaction biphasic; delayed liver edge extended to navel and was firm, with irregular surface; spleen not palpated; no ascites.
Nov. 18	++ (1:32)	+	++			
Nov. 19	++ (1:16)	+				Liver biopsy† showed acute stage of alcoholic cirrhosis with marked cellular necrosis and leukocytic reaction (chiefly polymorphonuclears); moderate amount of fat vacuolization; some fibrosis already present.
Nov. 20	+	±				
Nov. 27	±	+	+			
Dec. 4	—	±				
Dec. 20	—	±	++			Liver smaller; not so firm and not tender; second liver biopsy† showed that fat had largely disappeared and majority of liver cells appeared normal whereas very few had appeared normal on first examination; polymorphonuclears still present but markedly decreased in number; fibrosis remained unchanged.

*Treatment consisted of bed rest, high protein, high vitamin diet and cholinechloride.

†Performed by Dr. Wade Volwiler.

cent positive results with the urobilinogen test and of 37.86 per cent positive tests with the cephalin-flocculation method. Comparison between the cholic acid tests and the urobilinogen tests in these patients reveals equal tests in 77.88 per cent. Surprisingly, the cholic acid test was more sensitive than the urobilinogen test in 14.55 per cent, whereas the urobilinogen test was more sensitive in only 7.57 per cent of the cases.

It is of interest that in nonhabitual drinkers twelve to twenty-four hours after an excess of alcohol the modified Hay test and also the urobilinogen test may become positive. On the other hand, Hay tests on approximately 250 patients in my practice and in the Boston Dispensary Medical Clinic with the modified technic showed ± and even + results in patients without apparent liver lesion.

The serial examinations shown in Table 1 may demonstrate the value of the urobilinogen test and the cholic acid test in comparison with the cephalin-flocculation test, the blood bilirubin test, the clinical picture and liver biopsies. This case shows

drops or more were needed the test was rated ++.

Of 150 examined specimens on 150 patients 118 (78.67 per cent) were negative, 12 (8 per cent) were +, and 20 (13.3 per cent) were ++ (6 drops to 10 drops were needed). This means that in 21.33 per cent of the specimens examined slight bilirubinuria as a sign of damage to the liver cells was present although none of the patients had a visible jaundice. The methylene blue test gives almost the same percentage of positive findings in alcoholic patients as the cholic acid test. The comparison of the methylene blue test with the urobilinogen test made in the same patient shows a definite superiority of the latter.

SUMMARY AND CONCLUSIONS

In studies on large unselected groups of alcoholic patients at the Washingtonian Hospital parenchymal liver damage was demonstrable by the cephalin-cholesterol-flocculation test in 37.86 per cent of 140 specimens examined, by the quantitative urobilinogen test on the urine in 30.15 per cent of 2308 specimens examined, by the methylene blue

LIVER-FUNCTION TESTS IN ALCOHOLIC PATIENTS*

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IT HAS been believed for decades that chronic alcoholism damages the hepatic parenchyma and may finally lead to cirrhosis of the liver. Available statistics show alcoholism to be an etiologic factor in hepatic cirrhosis in 33 to 87 per cent of the cases. The extent to which the damage to the liver cells caused by alcohol is demonstrable by liver-function tests is of interest. Numerous authors, using the urobilinogen test, the blood bilirubin test, the bilirubin retention test, the bromsulfalein test, the galactose tolerance test and the cephalin-cholesterol-flocculation test found positive results in 20 to 50 per cent of uncomplicated cases of alcoholism. Almost all these reports are based on a relatively small number of cases.

It has been possible to study liver-function tests on a large number of unselected alcoholic patients of the Washingtonian Hospital, an institution specializing in rehabilitation and treatment of male alcoholic patients.

The patients came into the hospital in a state of acute intoxication, some of them after repeated admissions. In only a small percentage of cases was the liver palpable below the costal margin. None of the patients were jaundiced. Delirium tremens was encountered in only 3 per cent of the cases.

In the present study the cephalin-cholesterol-flocculation test of Hanger, the quantitative urobilinogen test in the urine of Wallace and Diamond, the Hay test for cholic acid excretion in the urine and Franke's methylene blue test for bilirubin in the urine were used.

One hundred and forty cephalin-flocculation tests were done on 140 patients with ripened emulsion (Mateer,^{1 2}), and readings were made after twenty-four and forty-eight hours. Twenty-five tests—that is, 17.86 per cent—were + in the forty-eight-hour reading, which is the decisive one, 28 tests, or 20 per cent, were ++ to ++++. *In toto*, in 37.8 per cent of examinations, evidence of damage to the liver was demonstrable by the cephalin-flocculation test. These figures are markedly higher than the figure of 20 per cent of positive tests in 40 alcoholic patients found by Wade and Ehrenfest-Richman.³ However, they stand in good agreement with the figures of former authors, who used various other liver-function tests in alcoholic patients.

The second test used was the quantitative estimation of urobilinogen in the urine (Wallace and Diamond⁴). The test was rated as + when the pink color was still seen in the dilution of 1:3 to 1:15,

and as ++ when the color disappeared in dilutions of 1:16 to 1:80. Higher necessary dilutions were recorded as +++.

Examinations of 2308 specimens of urine of 2070 patients gave the following results: in 30.16 per cent, the tests were indicative of liver-cell damage—+ in 18.15 per cent, ++ in 9.45 per cent and +++ in 2.56 per cent. These results are in agreement with the figures of positive urobilinogen tests in uncomplicated alcoholism found by other authors.

The largest amounts of urobilinogen seen were 1:300, 1:400, 1:450, 1:540, 1:650 and 1:750. It is surprising that in the cases with +++ reactions an enlarged liver was present in only 33.3 per cent. Serial examinations showed that in all groups considerable variations were sometimes noted from day to day. In 44 cases comparative tests were made of the morning and afternoon specimens. In 43.2 per cent the tests were the same at both times. In 36.3 per cent there was an increase in the afternoon specimen, and in 20.5 per cent there was a slight decrease. The afternoon increase could be as marked as follows: forenoon, ±, afternoon, 1:200; forenoon, 1:50, and afternoon, 1:200.

A comparison of the urobilinogen test and the cephalin-flocculation test made in the same patient shows a good correspondence in 54.64 per cent of the cases. However, it is surprising that in 36.08 per cent the urobilinogen test was positive whereas the cephalin-flocculation test was negative. In only 9.28 per cent the cephalin-flocculation test was positive, and the urobilinogen test was negative. The urobilinogen test seems to be more sensitive in acute transient damage to the liver cells, which apparently occurs often in alcoholic patients.

The third test used in this study was Hay's test for cholic acid excretion in the urine. This test is based on the lowering of the surface tension by cholic acids usually measured by the stalagmometric method. Simpler and for practical purposes equally accurate is the Hay test: dried sulfur depuratum powder strewn on the surface of the urine sinks to the bottom of the container when cholic acids are present. Mueller,⁵ Lepehne,⁶ Doumer⁷ and others recommended this test as very useful, though it is not a specific one. I modified the test by acidifying the urine with concentrated hydrochloric acid according to Morrison and Swalm,⁸ who recommended the addition of hydrochloric acid for their stalagmometric method. It was found that the Hay test became considerably more sensitive. The test was called ± when a small amount of the sulfur powder sank to the bottom within three to

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CONJUNCTIVAL AND CORNEAL CALCIFICATION IN HYPERCALCEMIA*

Roentgenologic Findings

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DEPOSITION of calcium or true ossification in the eyeball has been known to the ophthalmologist and pathologist. These conditions occur most commonly in the choroid and are believed to be often caused by injury. Twining and Shanks¹ distinguished four groups of intraocular calcifications as seen roentgenologically: calcification of the lens, ossification of the vitreous, calcified atheroma of the ophthalmic artery and a shrunken calcified globe. Kautz and Schwartz² described, in detail, the x-ray appearance of the ring-shaped calcific deposits in the choroid and also listed and discussed the differential diagnosis of other opacities in the orbit and globe, such as calcium deposits in retinoblastoma in children, opaque and semi-opaque foreign bodies, vascular calcifications, phleboliths, orbital angioma and osteoma.

Walsh and Howard³ have found, by ophthalmologic methods, calcification of the eye in patients with hypercalcemia. In their report, describing their own experience over ten years at the Johns Hopkins Hospital and similar observations by Dr David Cogan⁴ of the Massachusetts Eye and Ear Infirmary, they list 16 cases in which 7 patients presented the clinical picture of hyperparathyroidism, 7 vitamin D poisoning, and 2 sarcoidosis.

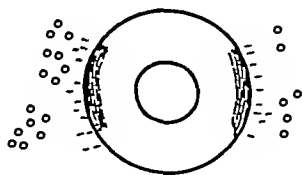


FIGURE 1 Corneal and Conjunctival Calcifications As Found on Ophthalmoscopic Examination of the Left Eye

The lesions, identified with the aid of the slit lamp, are of two distinct types: one in the conjunctiva, and the other in the cornea (Fig 1). The conjunctival lesions appear as small glass-like particles within the conjunctiva of the palpebral-fissure region. These minute areas are crystal clear. They may be many or few. The second type of ocular abnormality occurs in the cornea. It consists of hazy, grayish, granular epithelial and subepithelial

opacities running concentrically with the limbus on either the nasal or the temporal side or both. The opacity is most dense at the periphery, fading out centrally. Its appearance is similar to that of band keratitis seen in association with intraocular inflammation or rarely as a primary disorder. Chemically, these deposits are identified by conjunctival biopsy as probably consisting of calcium phosphate. The roentgenologic visualization of these ocular calcifications is the subject of this report.

CASE REPORT

A. E. S., (B. I. H., M4364),§ a 42-year-old man, had had crippling polyarthritis for 20 years and had received vitamin D medication since 1942, including 2 or 3 Ertron capsules daily, 3 or 4 tablets of Darthrone daily for 6 months and Dolcin tablets for several months. In 1943 a right ureteral colic had occurred, with hematuria and passage of "gravel." There were several similar episodes in the following year. When the patient was seen on January 14, 1949, he complained of a dull pain in the left costovertebral angle and gross hematuria. X-ray examination of the abdomen revealed bilateral calcification of the kidneys. On the basis of the history and these findings he was admitted to the hospital for further study.

Physical examination showed an edentulous patient with moderate pallor of the oral mucosa and the skin. The thyroid gland was enlarged to about three times the normal size and contained several nodules. The chest roentgenograms revealed bilateral changes in both upper lobes, consistent with arrested tuberculosis of the hematogenous type and moderately advanced emphysema. Destructive joint changes consistent with advanced rheumatoid arthritis were found in the fingers, wrists, elbows, shoulders, knee joints, left hip and spine. There was marked generalized decalcification of the bones, especially the long bones, with loosening of the cortices, but without cyst formation. There was in addition evidence of marked muscular wasting.

The kidneys, which were rather small, were normal in shape and position. There was extensive mottled calcification throughout both kidneys, the individual calcium flecks being 3 mm and smaller. The distribution of the calcification followed the individual pyramids of the kidney, with less calcification in the left kidney. Intravenous urography and retrograde pyelography revealed delay in excretion, marked impairment of concentration and slight dilatation of the calyces. These examinations also confirmed the intraparenchymatous location of the calcific deposits. In a complete survey, no soft-tissue calcification was found in the extremities or the walls of the chest and abdomen.

An ophthalmologic consultant reported as follows (Fig 1)

There is no redness in either eye. The corneas and conjunctivas look normal microscopically. The anterior chambers, pupils and tensions are normal. The lenses and vitreous are clear. The disks, maculae and retinal vessels appear normal. Vision is about 20/25 in each eye. Slit-lamp examination reveals grayish-white, powdery opacities along the limbus of the cornea, both temporally and nasally, from about 2-5 and 7-10 o'clock. The opacities are not deep, with only rare superficial blood vessels and about 15 to 10 mm wide. Otherwise, the corneas are clear.

§A complete discussion of the metabolic and hormonal aspects of this case will be published elsewhere by Drs. Mark F. Lessem and S. L. Gargill.

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test for bilirubinuria in 21.33 per cent of 150 specimens examined, and by the sulfur test for cholic acids in the urine in 19.40 per cent of 660 specimens examined. These figures are consistent with the results of former authors who made various liver-function tests in alcoholic patients, and reveal clearly that there is no regular correspondence between the four tests. In the acute stages the urobilinogen test and the cholic acid test seemed to be more sensitive than the cephalin-flocculation test. Sometimes, the cholic acid test was more sensitive than the urobilinogen test. In the more subacute and chronic stages the cephalin-flocculation test was sometimes the only positive one. A good screening method for office practice to detect early disturbance of the liver is the simultaneous performance of the qualitative urobilinogen test, the modified sulfur test for cholic acids and the methylene blue test for bilirubinuria. The urobilinogen test should be done preferably in the afternoon specimen. Examination showed, confirming numerous previous observations, that in 36.6 per cent of cases the afternoon excretion of urobilinogen exceeded considerably the morning excretion.

Furthermore, it can be concluded that the liver dysfunction in alcoholic patients can be largely transient. Even serious damage as found in the liver biopsy described can subside within a month. The occurrence of marked cirrhosis is surprisingly rare among the patients of the Washingtonian Hospital. This corresponds well with the opinion that hepatic cirrhosis develops only if several different factors have been present. The combination of the modern treatment of alcoholism by the conditioned reflex and psychiatric methods with an early modern anticirrhotic therapy may prevent

the development of hepatic cirrhosis in these patients (Thimann¹²).

I am indebted to Dr. J. Thimann, medical director of the Washingtonian Hospital, for giving me the opportunity to make this study, and to Dr. Fred M. Meyer and Mr. J. Stimson for their valuable help in these examinations.

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owski, Winkler and Peters,⁶ McLean and Lebo⁷ and Freeman, Roads and Yeager⁸) Similarly, Howard and Meyer⁹ noticed a recession of the ocular calcifications in 4 of 8 cases within one to sixteen months of withdrawal of vitamin D, often associated with, but not always parallel to, general clinical improvement

Dr Fuller Albright, who saw the patient in consultation, summarized his opinion as follows

There are at least three sequences that could have led to the present picture primary hyperparathyroidism, with hypercalcemia, nephrocalcinosis, renal insufficiency, rising serum phosphorus and falling serum calcium, rheumatoid arthritis, with immobilization, osteoporosis of disuse, hypercalcuria, nephrocalcinosis and so forth, and vitamin D overdosage, with rising serum calcium, nephrocalcinosis and so forth

The fact that stones antedated vitamin D therapy is against the third sequence and consistent with the first two The fact that abnormal calcium is confined to the eyes and kidneys is also somewhat against vitamin D overdosage. I favor primary hyperparathyroidism There is probably little to be gained by total removal of the parathyroid tumor, since the degree of renal insufficiency requires an increased compensatory production of hormone, greater than the tumor is now making The diagnosis can be made only by exploration

The patient was explored, but no parathyroid tumor was found in the neck

SUMMARY

A case of hypercalcemia is reported, the etiology of which is not yet certain Primary hyperparathyroidism, immobilization secondary to rheumatoid arthritis or vitamin D poisoning possibly played a role in the etiology

Roentgenologic examination of the anterior portion of the eyeballs revealed calcification of two different types corresponding to the two types described by Walsh and Howard, found by ophthalmoscopic examination, but not yet described in the roentgenologic literature

The bone-free x-ray technic used in this examination is described in detail

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AGRANULOCYTOSIS FOLLOWING PYRIBENZAMINE*

Report of a Case

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THE effectiveness of Pyribenzamine (tripelenamine hydrochloride) in many allergic states and its apparent freedom from toxicity have led to its widespread use with little fear of serious reaction. Thus far only 1 case of depression of the granulocytic series after Pyribenzamine therapy has been reported.¹ The following case is believed to represent agranulocytosis resulting from the use of Pyribenzamine over a period of five and a half weeks.

CASE REPORT

A 39-year-old housewife entered the hospital complaining of sore tongue and mouth of 3 days' duration. The past history included migraine headache since the menarche, for which she had frequently used empiric compound. There was no history of eczema, hay fever, asthma or other allergic reactions to foods or drugs until 2 months before admission,

when she had noted a red, itching rash on the left forearm spreading to involve the trunk. This rash was diagnosed as a contact dermatitis. Seven weeks before entry she was treated with Benadryl, lotions and salves without effect. Five and a half weeks before admission the hemoglobin concentration was 15.7 gm per 100 cc., and the blood smear was normal. Medications were changed to Pyribenzamine, 50 mg three times daily, chloral hydrate for sleeplessness and Ergotrate (ergonovine maleate) for her headaches. On this program the rash and itching subsided. Three and a half weeks before entry the Pyribenzamine dosage was reduced to 25 mg three times daily.

She had used no medication except Pyribenzamine for at least a week preceding the onset of the present illness. Three days before admission she became ill with mild chills, malaise, generalized aches, prostration, sore mouth and a temperature of 100°F. On the next day she omitted the Pyribenzamine and took several empiric tablets. Two days before admission ulcerations appeared on her tongue, her gums became swollen, and she complained of an unpleasant taste. She had no sore throat. From then until admission the mouth and tongue became progressively more painful, and she took food and fluids with increasing difficulty. Treatment consisted of mouth rinses with salt, sodium bicarbonate and milk of magnesia. On the afternoon of admission the white-cell count was 1700, with 2 per cent neutrophils in the stained smear. She was given 300,000 units of penicillin in heeswax and oil intramuscularly, and was referred to the hospital. During the 5½ weeks preceding her illness, she had taken a total of 40

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The bulbar conjunctivas in the interpalpebral spaces show occasional small, round and oval, glistening superficial, slightly elevated "cysts" or crystals. Some are single and isolated, others are grouped together. In addition to these shiny spots, there are rare nonglistening deposits under the conjunctiva, with no enlargement or newly formed blood vessels. These changes are identical in both eyes. This microscopical eye picture agrees with that described in patients with hypercalcemia.

Examination of the urine showed a +++ test for albumin, with a specific gravity of 1.010, ++ to +++ tests for calcium were repeatedly demonstrated by the Sulkowitch method while the patient received a low-calcium diet. Sputum and urine examinations for tubercle bacilli by smear, culture and guinea-pig inoculations were negative. Morphologic blood studies showed a moderate anemia, with a red-cell count of 3,500,000 and hemoglobin of 10.1 to 12.9 gm per 100 cc, and were otherwise normal. The nonprotein nitrogen of the blood ranged from 50 to 79 mg per 100 cc in 14 examinations. Five total-protein examinations were 6.15 to 7.45 gm per 100 cc. Seventeen calcium determinations ranged from 10.7 to 11.6 mg per 100 cc and dropped to 8.7 to 9.1 mg per 100 cc after treatment with stilbestrol, saline infusions and Amphojel. Twelve inorganic serum phosphorus determinations showed values of 4.5 to 4.7 mg per 100 cc before treatment and values of 2.9 to 2.3 mg per 100 cc after treatment. The alkaline phosphatase ranged from 2.4 to 3.1 Bodansky units.

Skull roentgenograms disclosed faint calcification in annular arrangement in the orbits (Fig. 2). With the bone-free technic,

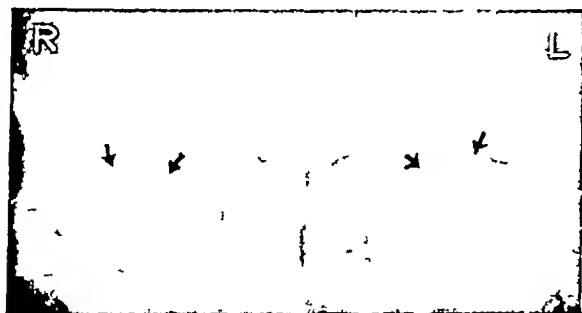


FIGURE 2 Portion of a Posteroanterior Roentgenogram of the Skull

The white, curved lines in the orbits (arrows) represent the corneal calcifications. (The white spot above the left orbit is due to a buckshot beneath the skin.)

described below, these calcifications were brought into better relief. They were of two different types. When the scleral portion of the globe was hit tangentially plump, rod-like calcific deposits 2 mm in width and 3 or 4 mm in length in a curvilinear arrangement were seen. If the corneal limbus was hit tangentially a solid, homogeneous, dense calcific

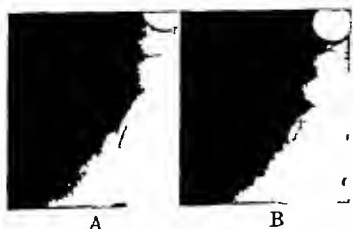


FIGURE 3 Two Tangential Views of the Left Globe (Bone-Free Technic) Demonstrating the Corneal Calcification (A) and the Conjunctival Calcifications (B). (The white spot above the left orbit is due to buckshot beneath the skin.)

shadow of less than 1 mm in width and 7 mm in length was seen in the left eye (Fig. 3), and an interrupted similar shadow line 8 mm in length was seen in the right eye.

In the bone-free technic standard dental films are used. The patient, conveniently seated in a dental chair, presses the film with two fingers of the opposite hand close to his nose in the medial corner of the eye. The tube of the dental x-ray machine is centered toward the external canthus from behind in such a way that the beam covers as much of the eyeball as possible. The patient keeps his eye open and is directed to look steadily alternating to the side, straight forward and medially, in order that several tangential views of various parts of the anterior convexity of the globe may be obtained. The technical factors are the same as those for frontal teeth, 15 MA, 55KV and 1 second were the technical factors used with our equipment.

DISCUSSION

The roentgenologic findings of calcification of the conjunctiva and cornea in the palpebral fissure can easily be correlated with the ophthalmoscopic findings of Walsh and Howard,³ observed also in the case reported above. Roentgenologically, two types of calcification have been identified. The short, rod-like deposits are apparently identical with the crystal-clear, nodular deposits found in and beneath the conjunctiva, the linear shell-like deposits correspond to the calcification in the limbus. The observations of Walsh and Howard, as well as those of Cogan,⁴ were made exclusively in patients with hypercalcemia of various origin.

In this case, too, the ocular calcification is apparently a manifestation of hypercalcemia though the cause of the hypercalcemia is not definitely determined. Three causative factors were considered: hyperparathyroidism, vitamin D poisoning and immobilization due to rheumatoid arthritis.

Widespread metastatic calcifications have been observed in all three of these conditions (Mulligan⁵). However, the calcium deposits in many organs, such as the lung, heart, stomach, liver and spleen, can be recognized only by pathological examination of the tissues. Calcifications of the kidneys, periarticular structures and subcutaneous tissue, as well as arterial calcifications, of diagnostic value solely in young persons, have been the only ones accessible to roentgenologic exploration. Renal and vascular calcifications have been found with great frequency in all three of these conditions, whereas periarticular calcium deposits, rather common in excess of vitamin D, are but rarely reported in hyperparathyroidism and hypercalcemia secondary to bone and joint disease. The generalized moderate decalcification of the bones occurs in all three conditions and has no differentiating significance in the presence of considerable renal damage. Disappearance or marked diminution of massive deposits of lime salts have been observed after withdrawal of vitamin D medication with or without simultaneous reduction of calcium intake (Dan-

onset of menstruation was a predisposing factor in the precipitation of agranulocytosis. In the case reported above, it is interesting that the acute symptoms began two days after the beginning of the period.

SUMMARY

A case representing agranulocytosis following pyribenzamine is presented. This is the second case report of this condition subsequent to the administration of Pyribenzamine and calls attention to the advisability of performing white-cell counts on any patient receiving Pyribenzamine for prolonged periods who shows signs or symptoms of agranulocytosis.

Since the preparation of this report Drs George A McCormack and Richard G Whiting have informed us of a similar case treated at the Lawrence Memorial Hospital in Medford. Their patient took approximately 400 mg of Pyribenzamine for a month prior to the onset of agranulocytosis. On the sixth day after the onset of this patient's illness the white-cell count had declined to 1100, and the neutrophils had completely disappeared. The patient made an uneventful recovery.

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MEDICAL PROGRESS

RH AND OTHER BLOOD GROUPS*

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THE Rh and other blood groups have achieved great importance in the last few years because of their relation to erythroblastosis fetalis. But numerically this disease may not emphasize the need for practical knowledge about blood groups as often as blood transfusion does—a therapeutic procedure that has become relatively simple and used, or sometimes possibly abused, probably several million times a year. In addition, genetic and anthropologic studies using blood-group characteristics have been revitalized by the discovery of the newer and now much more numerous blood agglutinogens. And finally, medicolegal problems, which formerly were unsolvable because of too few positive detectable characteristics for identification of any person's blood-group individuality, can now come closer to satisfactory resolution because of the possible permutations and combinations of the blood-group factors, making any blood more nearly unique.

By use of knowledge and technics now available, the safety of multiple transfusion of whole blood has been greatly increased. Relatively simple laboratory tests are now available to establish accurately the compatibility of the blood of the donor and the recipient.

The discovery of the Rh factor in 1939 by Levine and Stetson,¹ who found the Rh antibody in a parturient woman after a hemolytic transfusion reaction, and independently in 1940 by Landsteiner and Wiener,² who found the Rh antibody in a rabbit immunized by Rhesus-monkey blood, opened the door to re-exploration of blood groups. This subject has been reviewed recently.³⁻⁶ Seven different blood-group systems are now known in which the antigens are common enough to be useful in such studies, and these seven systems are probably controlled by seven different pairs of chromosomes.

This report briefly reviews the field of blood groups, giving only the basic information. The blood-group antigens and antibodies are discussed briefly, with emphasis on genetic and immunologic factors. Certain important clinical considerations will be discussed in relation to some of the antigens. The paragraphs on technic are brief. More complete studies have been published elsewhere.^{3,9} A later review will cover the clinical aspects of the subject.

ANTIGENS AND ANTIBODIES OF HUMAN BLOOD GROUPS

The blood groups are named for the specific antigenic substances (agglutinogens) in the red blood cells. These antigens are inherited factors, appearing early in fetal life and remaining unchanged throughout life. Table 1 lists most of the known antigens that are recognizable in the blood groups and subgroups. Certain rare antigens, and identifiable variants other than those listed below in-

*Adapted from *A Syllabus of Laboratory Examinations in Clinical Diagnosis*. Printed by permission of the Harvard University Press. From the Blood Grouping Laboratory of Boston and the Children's Medical Center and the Department of Pediatrics, Harvard Medical School.

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gm of Pyribenzamine. She had had a normal menstrual period beginning 2 days before the onset of her illness.

Physical examination showed a well developed and well nourished woman complaining of a sore mouth but appearing only moderately ill. There were two small ecchymotic areas on the lateral surface of the right forearm. There were no petechiae. The eyes, ears and nose were normal, including funduscopic examination. The breath was not remarkable. There was generalized swelling of the gums, with several areas of hemorrhage and necrosis of the papillae. On the sides of the tongue were three deep, punched-out necrotic ulcerations measuring about 5 mm in diameter and covered with yellow exudate. There was no surrounding inflammation. The pharynx and tonsils were normal. There was an enlarged tender anterior cervical lymph node on the right. The heart and lungs were normal. The liver edge was palpable 4 cm below the right costal margin in the midclavicular line on deep inspiration, its upper border being in the sixth interspace, to percussion. It was nontender. The tip of the

enlarged. The patient was asymptomatic and had refrained from using any medication. The red-cell count was 4,630,000, with a hemoglobin of 14.3 gm, and the white-cell count 8700, with 73 per cent neutrophils, 20 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils.

DISCUSSION

During the five and a half weeks preceding her illness the patient had taken four medications: Pyribenzamine, Ergotrate, empirin compound and chloral hydrate. However, for a week or more before the onset of her illness, she had used nothing but Pyribenzamine, omitting the others because she felt so well. She did not use empirin again until a day after the onset of her sore mouth, when

TABLE 1 *Effect of Therapy on Neutropenia in a Case of Agranulocytosis Following Pyribenzamine*

DAY	TREATMENT		WHITE CELL COUNT	NEUTROPHILS	BAND FORMS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	BASeOPHILS
	PENICILLIN units/day	FOLIC ACID mg/day		%	%	%	%	%	%
1	—	—	1 700	2	—	—	98	—	—
1	600 000	—	3 200	8	6	34	52	—	—
2	800 000	—	5 300	24	—	50	24	2	—
3	800 000	10	4 400	34	—	44	22	2	—
4	800 000	10	6 000	57	2	28	12	1	—
5	800 000	10	5 300	56	—	32	7	—	— (Myelocytes, 4% metamyelocytes 1%)
6	400,000	10	6 300	56	11	23	6	1	— (Myelocytes 2% metamyelocytes 1%)
7	300 000	10	5 600	62	1	30	5	2	—
8	300 000	10	7 500	70	—	27	3	—	—
9	—	—	7 600	75	1	19	5	1	—

spleen was felt below the costal margin on deep inspiration. The extremities were normal. Neurologic examination revealed no abnormalities.

The temperature was 102°F, the pulse 112, and the respirations, 18, the blood pressure was 118/70.

The urine was yellow, acid and clear, with a specific gravity of 1.020, and with negative tests for albumin, sugar, bile and acetone. Microscopic examination of the sediment showed normal results. A stool was brown and guaiac negative. A blood nonprotein nitrogen taken on the 2nd hospital day was 29 mg per 100 cc. The blood Hinton and Kahn tests were negative. A heterophil-antibody agglutination on the 3rd hospital day was negative in all dilutions. The prothrombin time was 16.7 seconds, with a control of 15.0 seconds. Four hemoglobin determinations (Sahli) ranged from 13.4 to 16 gm per 100 cc. Four red-cell counts ranged from 4,180,000 to 4,500,000. The platelets were normal. The white-cell count on the evening of admission was 3200, with but 8 per cent neutrophils and 6 per cent band forms. On the next day the white-cell count had risen to 5300, with 24 per cent neutrophils. Thereafter the total neutrophil count rose as shown in Table 1.

The patient received intramuscular injections of penicillin in doses of 100,000 units every 3 hours for 6 days, and 100,000 units every 8 hours for a total dosage of 4,800,000 units. Supportive treatment included a soft diet and 2 multivitamin capsules daily. On the 3rd hospital day folic acid, 10 mg daily, was added. The patient was febrile for the first 2 hospital days, the temperature reaching 101.4°F on the 2nd day, after which it remained normal. This fall in temperature was paralleled by a decrease in the pulse rate and coincided with marked improvement in the general well-being of the patient. The lesions in the mouth healed slowly but steadily so that at discharge, 8 days after admission, the gums were virtually normal and the ulceration on the tongue was clean, with epithelializing, small concavities. The spleen receded on about the 4th hospital day.

Examination two months after the acute illness revealed irregular depressions at the sites of the former ulcerations on the tongue. The spleen was not palpable. The liver was not

she omitted Pyribenzamine for the first time in five and a half weeks after having taken a total of 40 gm of the drug. On the basis of the history, Pyribenzamine seems to be incriminated. The depression of the granulocytes that occurred in this case only after prolonged exhibition of the Pyribenzamine seems analogous to the leukopenia seen after extended use of other drugs, such as the sulfonamides, thiouracil or propylthiouracil. In all these agents the effect on the granulocytic series is not manifest in the early days of the administration of the drug. Wintrobe² states that the granulocytopenia from sulfanilamide usually occurs after one to three weeks of treatment, and that from thiouracil usually after four to eight weeks. It seems that the analogous time for Pyribenzamine is four to five weeks. In the case previously reported¹ granulocytopenia occurred after eight weeks of Pyribenzamine.

Although folic acid was used in therapy, we do not believe that it played a role in recovery, since the rise in the white-cell count had begun before folic acid was started. The significant monocytosis observed initially and in subsequent examinations (Table 1) may be considered evidence of the onset of spontaneous recovery, according to the observations of Reznikoff.³

Thompson⁴ reported cyclic neutropenia just preceding the menstrual flow, and he believed that the

higher titer in serum medium than in saline solution or in albumin and is difficult to neutralize with soluble antigen.⁶ The immune anti-A antibodies so far described have been much more active against A₁ than against A₂ cells. A small proportion of the cases of erythroblastosis fetalis are caused by immune anti-A or anti-B, but it is definitely known that the Group A or O mother of a Group B fetus

wise, the genotype BB cannot be distinguished serologically from the genotype BO.

The CDE (Rh) System

Seldom has a subject caused so much confusion in the minds of both physicians and laity as that of the Rh factor. Much of the confusion appears to result from the rapidity of progress in the field

TABLE 4 The Rh System

SUBGROUPS AMONG BRITISH POPULATION*		GENOTYPES AMONG BRITISH POPULATION*				AGGLUTINATION BY ANTISERUMS				
WIENER NOMEN CLATURE	FREQUENCY c%	(FISHER- RACE)	(WIENER MODIFIED)	CALCULATED FREQUENCY c%	anti-C (anti-Rh')	anti-D (anti-Rh)	anti-E (anti-Rh')	anti-c (anti-Hr')	anti-d (anti-Hr)	anti-e (anti-Hr')
					70c%	85c%	30c%	80%	63c%	97%
rh	15.1	cde/cde	r r	15.1020	0	0	0	+	+	+
rh'	0.8	Cdc/Cdc Cdc/cde	R' R' R' r	0.0097 0.7644	+	0	0	+	+	+
Rh ₁	2.1	cDe/cDe cDe/cdc	R ₁ R ₁ R ₁ r	0.0659 1.9930	0 0	+	0 0	+	+	+
rh'	0.9	cdE/cdE cdE/cdc	R'' R'' R'' r	0.0141 0.9235	0 0	0	+	+	+	0 +
Rh ₁	53.4	CDc/CDc	R ₁ R ₁	17.6803	+	+	0	0	0	+
		CDc/Cdc	R ₁ R	0.8270	+	+	0	0	+	+
		CDc/cDe	R ₁ R ₁	2.1583	+	+	0	+	0	+
		CDc/cdc	R ₁ r	32.6808	+	+	0	+	+	+
		Cdc/cDe	R R ₁	0.0505	+	+	0	+	+	+
Rh ₂	14.1	cDE/cDE	R ₂ R ₂	1.9906	0	+	+	+	0	0
		cDE/cDe	R ₂ R ₁	0.7245	0	+	+	+	0	+
		cDE/cdE	R ₂ R'	0.3323	0	+	+	+	+	0
		cDE/cde	R ₂ r	10.9657	0	+	+	+	+	+
		CdE/cdE	R ₂ R	0.0610	0	+	+	+	+	+
rh rh'	0.03	CdE/CdE	R ₂ R ₂	0.0000003	+	0	+	0	+	0
		CdE/Cdc	R ₂ R'	0.0001	+	0	+	0	+	0
		CdE/cdE	R ₂ R	0.0001	+	0	+	+	+	0
		CdE/cde	R ₂ r	0.0039	+	0	+	+	+	+
		Cdc/cdE	R' R'	0.0234	+	0	+	+	+	+
Rh ₁ Rh ₂	13.6	CDE/CDc	R ₂ R ₂	0.0006	+	+	+	0	0	0
		CDE/CDc	R ₂ R ₁	0.2048	+	+	+	0	0	+
		CDE/cDE	R ₂ R ₁	0.0687	+	+	+	+	0	0
		CDE/CdE	R ₂ R ₂	0.00002	+	+	+	0	+	0
		CDE/Cdc	R ₂ R'	0.0046	+	+	+	0	+	+
		CDE/cDE	R ₂ R ₂	0.0042	+	+	+	0	+	+
		CDE/cDe	R ₂ R ₁	0.0123	+	+	+	+	0	+
		CDE/cdE	R ₂ R ₁	11.8648	+	+	+	+	0	+
		CDE/cdE	R ₂ R	0.0058	+	+	+	+	+	0
		cDE/CdE	R ₂ R ₂	0.0014	+	+	+	+	+	0
		CDE/cde	R ₂ r	0.1893	+	+	+	+	+	+
		CDE/cdE	R ₂ R'	0.9992	+	+	+	+	+	+
		CdE/Cdc	R ₂ R'	0.2775	+	+	+	+	+	+
		CdE/cDe	R ₂ R ₁	0.0003	+	+	+	+	+	+

*Based on data of Race et al.¹¹ (the frequency of the R₂ gene is taken as 0.00005) and Fisher and Race¹² (the frequencies are approximately the same for American whites the proportion of D-negatives being a little lower — approximately 15 per cent).

can have immune anti-B in her serum without any observable ill effects on the baby.

Anti-A and anti-B typing serums. The apparent discrepancy between the number of identifiable phenotypes and known genotypes in the ABO system (Table 3) is explained by the limited number of specific antisera as follows. Anti-A serum agglutinates all Group A and Group AB cells. Anti-A₁ (anti-A serum absorbed with A₂ cells) does not agglutinate A₂ or A₂B cells, but does agglutinate A₁ and A₁B cells. Anti-B serum agglutinates only B and AB cells. The person of genotype A₁A₂ can be differentiated only by family studies, not by direct testing, from the A₁A₁ or A₁O person, and all three have therefore the same phenotype. Like-

and from the complex terminology. The antigens and antibodies are not confusing if they are considered one by one, employing the nomenclature of Fisher and Race, which is based on assigning letters (C, D, E, c, d, e) to the specific antigens of the Rh system (Table 4). Although it is recommended that the CDE nomenclature be adopted as standard,¹⁷ the Wiener abbreviations are indispensable in conversation, and must be known if much of the literature is to be understood.

Genetics of the CDE system. According to Fisher's theory there are three sets of allelic (alternative) genes, C, C*, and c, D and d, E and e — one set for each of three loci in one of the pairs of chromosomes. The loci are closely, or absolutely, linked,

crease the number of possible genotypes* to well over 100,000,000

The ABO System

Antigens The A₁, A₂, B and O antigens are inherited as Mendelian alleles. The A and B antigens of the red cells were discovered by Landsteiner¹⁰ fifty years ago. That O is actually an antigen has only recently been recognized.¹¹ The variant A₂ has been known for many years.¹² The curious facts that virtually all B-negative adults have anti-B antibodies and that virtually all A-negative adults have anti-A antibodies in

who have large amounts of the antigens A or B, or both, in their saliva and gastric juice are called "secretors," and inherit this characteristic as a Mendelian dominant. Eighty per cent of Europeans are secretors.

Antibodies Anti-A and anti-B antibodies are naturally occurring substances. They agglutinate

TABLE 2 Simplified Summary of ABO System*

BLOOD GROUP (ANTIGENS OF RED CELL)	FREQUENCY OF BLOOD GROUPS IN UNITED STATES %	ISOAGGLUTININS IN SERUM†	RED CELLS THAT ARE AGGLUTINATED AND MAY BE HEMOLYZED BY SERUM
O	45	anti A and anti B	Groups A, B and AB
A	41	anti B	Groups B and AB
B	10	anti A	Groups A and AB
AB	4	—	—

*The phenotypes and genotypes are summarized in Table 3.
†Isohemolysis may be present.

TABLE 1 Known Antigens of Seven Different Systems of Blood Groups*

ANTIGENS	SYSTEM	PRESENTLY IDENTIFIABLE PHENOTYPES†	POSSIBLE GENOTYPES
A ₁ , A ₂ , B, O‡	ABO	6	10
{ C, C ^w , c D, d E, e	Rh	36	78
{ M, N S	MNS	6	10
P	P	2	3
Le ^a , Le ^b	Lewis	3	3
K, k	Kell	3	3
Lu ^a	Lutheran	2	3
Totals 20 antigens 7 systems		46,656	631,800

*A number of variants are omitted.

†Phenotype: the identifiable antigenic makeup of the red blood cells dependent on but not necessarily indicating the complete gene pattern.

‡Antigens shown in the same line are mendelian allelomorphs (alternative characters).

§Antigens in brackets are genetically linked.

their serum have not been explained on either genetic or immunologic grounds, but they are obviously of enormous importance as far as blood transfusions are concerned. The specificity of anti-B is quite uniform from one person to another, but there is considerable variation in anti-A antibodies, their activity against A₂ cells often being weak. Occasionally, anti-A₁ is found in the serum of an A₂ person.⁸ An antibody that agglutinates all O and A₂ red cells has been variously called "anti-O" and "anti-A₂," its exact significance is a matter of dispute. The relations between the antigens and antibodies in the ABO system are shown in Table 2.

The A and B antigens are rather widely distributed in nature, especially A, which is found in various animals and plants. Both antigens are easily obtainable in pure water-soluble form from extra-human sources (for example, A is obtained in high concentration from hog gastric mucosa) and have been used in concentrated solution for experimental purposes or for the neutralization of anti-A and anti-B in human whole blood or serum.¹³ The A and B antigens are also found, in various amounts, in other human tissues than the red cells. Persons

red cells containing the corresponding specific antigens. Agglutination does not require complement, is most active at 4°C, is active at 37°C and occurs with red cells suspended in saline solution, serum or a solution of albumin.

Isohemolysis and isoagglutinins may occur in the same serum. They are not separable, and differ in that hemolysis requires serum complement. Isoagglutinins are accompanied by isohemolysis in only about 30 per cent of possible cases.⁸ They

TABLE 3 The ABO System

PHENO TYPE	OBSERVED FRE QUENCY IN UNITED STATES* %	GENOTYPE	CALCULATED FREQUENCY† %	REACTIONS WITH TYPING SERUMS		
				anti-A	anti-B‡	anti-B
A ₁	41.0	A ₁ /A ₁	3.53	+	+	0
		A ₁ /A ₂	2.56	+	+	0
		A ₁ /O	25.30	+	+	0
A ₂		A ₂ /A ₂	0.46	+	0	0
		A ₂ /O	9.15	+	0	0
A ₁ B	4.0	A ₁ /B	2.94	+	+	+
		A ₂ /B	1.06	+	0	+
B	10.0	B/B	0.72	0	0	+
		B/O	9.28	0	0	+
O	45.0	O/O	45.00	0	0	0

*Data of Snyder¹⁴ on 20,000 Americans.

†Subgroups of ABO system based on Wiener's¹⁵ tests of 1077 white persons (New York).

‡Anti-A serum absorbed with A₁ cells.

are specifically neutralized by soluble A or B substance.

Immune anti-A and anti-B There is no evidence that natural anti-A or anti-B harms the fetus. In contrast to the natural anti-A and anti-B antibodies, "immune" antibodies have been described by Witebsky⁵ and found in numerous cases, as in a Group A or Group O woman carrying a Group B fetus. The immune anti-A or anti-B gives a

*Genotype is defined as the total gene pattern inherited from the parents, not necessarily identifiable by typing serum.

In this discussion of the peculiarities of the Rh antibodies, specific reference is made only to anti-D, since other antibodies in this group may behave in a similar fashion

An important contribution to the science of immunology was made by workers in the field of blood grouping when it was shown that agglutinins existed in different forms. It was first shown that certain anti-D antibodies might specifically coat D-positive cells without agglutinating them, to such an extent that the coated cells could not then be agglutinated by potent anti-D agglutinating antibodies^{20, 21}. Next, it was demonstrated that these antibodies, which were unable to agglutinate red blood cells in saline solution, the traditional medium for such tests, were able to agglutinate red cells in a medium of 20 per cent albumin²². Finally, it has been shown that albumin-active (saline-inactive) antibodies exist that are not "blocking" antibodies. This last type of antibody, representing perhaps a third "order" of antibodies, which coat but do not block red cells and do not agglutinate in saline solution, have been called "cryptagglutinoids"* by Hill, Haberman and Guy²³. Preliminary research by these authors²³ appears to show that the three "orders" of antibody are found in highest concentrations in three distinct protein fractions — gamma globulins (saline-active agglutinins), beta globulins (the albumin-active cryptagglutinoids), and euglobulins (blocking antibodies and cryptagglutinoids). "Agglutination" of red cells is observed, however, with all three "orders" of antibody, in saline solution, when the Coombs technic, using anti-globulin serums, is employed. The several varieties of anti-D antibodies are all specific in their relation to the D antigen and may all be present in the same serum. Their differences only accentuate the need for identifying them in serums presented for investigation. The *in vitro* activity of anti-D antibodies depends not on any quality of the particular D antigen involved, but solely on the antibody-forming mechanism of the sensitized person.

It is also suggested that the saline-active antibody cannot pass through the placenta, whereas the hyperimmune antibody readily passes through, to be found in the baby's serum (in the case of a D-negative baby) in concentration equal to that in the mother's serum.

The MNS System

The M and N antigens (mendelian alleles) were discovered by Landsteiner and Levine^{24, 25} in 1927. The S antigen is a recently discovered one²⁶ that is genetically linked to M and N. Since each of the three MN types may be positive or negative with respect to anti-S, there are six phenotypes, when anti-M, anti-N and anti-S are all used. Since an anti-s serum has not been discovered, the SS genotype

*O-₊ synonyms are hyperimmune antibodies, incomplete antibodies, fixators and blockers. Saline-active antibodies are also known as easily immune antibodies, complete antibodies and agglutinins.

type can be distinguished from the Ss genotype only by family studies. Even if anti-s were available, one could not distinguish except by family studies the two genotypes MS/Ns and Ms/NS (Table 5).

In human beings M, N, and S are relatively poor antigens. Natural anti-M and anti-N are observed occasionally in low titer. Such antibodies are usually if not always, agglutinins effective in the cold. Immune anti-M has been found in a number of cases in which Type N persons have been given transfusions of M or MN blood. The immune anti-M is active at 37°C, and may be the cause of a severe hemolytic transfusion reaction. Anti-S

TABLE 5 *The MNS System*

PHENO- TYPE	OBSERVED FRE- QUENCY IN ENGLAND*	GENOTYPE	CALCULATED FREQUENCY %	REACTIONS WITH TYPING SERUMS		
				anti-M	anti-N	anti-S
MS	20.9	MS/MS	6.53	+	0	+
		MS/Ms	14.26	+	0	+
Ms	7.41	Ms/Ms	7.74	+	0	0
		MS/NS	4.15	+	+	+
MNS	28.5	MS/Ns	19.68	+	+	+
		Ns/NS	4.52	+	+	+
MNs	22.1	Ms/Ns	21.45	+	+	0
NS	6.9	NS/NS	0.66	0	+	+
		Ns/NS	6.24	0	+	+
Ns	14.5	Ns/Ns	14.78	0	—	0

*Based on data of Pickles²⁷ in a study of 340 English bloods.

has not been identified as a natural agglutinin and has not been produced in animals. Several examples of immune anti-S in S-negative persons have been reported. In one such case the antibody failed to cause agglutination of S-positive cells, but did "coat" them as could be demonstrated by the Coombs test. Anti-M and anti-N typing serums are obtained by immunization of rabbits with human Type M and Type N blood.

Since clinical problems involving M, N and S are so uncommon, typing with anti-M, anti-N and anti-S is not necessary in routine examinations, although they must be kept in mind whenever clinical problems cannot be solved with the use of A, B and Rh serums.

The P System

The antigen P was discovered by Landsteiner and Levine²⁸ in 1927 when they found in the serum of a rabbit, immunized with human blood, an antibody that agglutinated about 75 per cent of all human red cells irrespective of their ABO and MN blood groups (Table 6).

No serum corresponding to the predicted anti-p has as yet been identified.

Anti-P is reported to be fairly frequent in P-negative human beings, as a naturally occurring weak

and crossing over has not yet been observed. The number of possible combinations that may occur is quite large (Table 4). The genes are given the same names as the antigens of the red cells. It is important to emphasize that the inheritance of these genes is as though they were all *mendelian dominants*. To state it more correctly, there is *no dominance*.

The C^w antiserum¹⁸ and the genotypes having this antigen have not been included in Table 4, since they are of no real clinical importance and their inclusion would complicate the table. The C^w antigen is an uncommon, but serologically and genetically distinct, variant of C. The antigens C, C^w and c are genetically related in the same way that A, B and O are related, as Mendelian allelomorphs. Therefore, all human beings can be divided into six genotypes — CC, CC^w, Cc, C^wC^w, C^wc and cc. It is only when the possible combinations at the C locus are multiplied by the possible combinations at the D locus (DD, Dd and dd), and then by the possible combinations at the E locus (EE, Ee and ee) that the system appears complicated.

Only when it becomes important to determine whether a person is homozygous for D (DD) or heterozygous (Dd) is it necessary to consider the Rh antigens as a group. This is necessary because no anti-d typing serum is available. Anti-C, anti-D, anti-E and anti-c serums are generally available, and can be used to determine with fair accuracy the "zygosity" for D of any given person. A brief examination of Table 4 will indicate how this is done. Predictions must be based on the statistical table unless blood relatives of the person in question are available for examination.

Immunologic considerations of the CDE (Rh) system. The antigens in the Rh system vary considerably in their antigenicity. Only D is a really effective antigen. Between 50 and 75 per cent of D-negative human beings develop immune anti-D antibodies if the attempt at immunization is sufficiently prolonged. About 50 per cent are immunized by a single transfusion of D-positive blood. About 5 per cent are immunized by pregnancies involving D-positive fetuses. The corollary to this last statement should be emphasized — namely, that 95 per cent of D-negative women with D-positive husbands (and D-positive fetuses) are never immunized (sensitized) to D, their infants will not have erythroblastosis.

The other antigens of the Rh system are very much less antigenic, although antibodies to each of them have been found in human serums at one time or another. A still unexplained phenomenon is the frequent occurrence of anti-C in a human serum that also contains anti-D, and the extreme rarity of occurrence of anti-C in the serum of a D-positive, C-negative person. This phenomenon suggests some basic immunologic relation between the anti-

gens D and C, so that the presence of the D antigen is protective against immunization to the C antigen. There is a similar, but less striking, relation between anti-D and anti-E antibodies, in that anti-E has been found in many D-positive, E-negative persons (though in most cases it is present along with anti-D), suggesting that the immunologic relation between D and E is less close than that between D and C. The relatively close relation of D to C has been postulated by Fisher on genetic grounds also. It is evident that the protective effect of the D antigen is not shared by either C or E, since D-negative persons having C or E or both appear to be as readily immunized by D as persons lacking both C and E. This problem deserves further study.

The over-all relative effectiveness of the Rh antigens is indicated by the fact that of all persons immunized by one or more of the Rh antigens, over 95 per cent have anti-D, a few have anti-c or anti-E, or both, and an extremely small fraction have anti-C alone, or anti-e or anti-d.

The D antigen, besides being the most important from the immunologic viewpoint, is also most variable. D-positive red cells from most persons are agglutinated by all anti-D typing reagents. About 1 per cent of D-positive red cells, however, are agglutinated by some anti-D serums and not by others. This 1 per cent comprises an apparently unlimited variety of peculiar D antigens. The symbol D^u has been given to this group of irregular D antigens,¹⁹ although the single symbol does not imply any specific immunologic or genetic characteristic of the antigen. Since the D^u variants are antigenic, they are clinically important, especially because they are difficult to recognize by routine typing methods. A fatal hemolytic transfusion reaction has resulted from the administration of such blood, thought to be D-negative, to a D-negative person who had previously been immunized by D. The D^u variants are inherited just as the other antigens of the Rh system are, and "breed true" genetically. The D^u antigens are, for clinical purposes, best considered as identical with the D antigen.

The D antigen has been demonstrated with certainty only in the red blood cells and in red-cell stroma. Experiments indicating that D is present in certain other body cells or fluids have not been confirmed.

The antibodies of the CDE (Rh) system. Isoagglutinins for the Rh factors do not occur naturally. When found in human serum, they result from active isoimmunization, either by transfusion of blood or by pregnancy. Anti-Rh isoagglutinins are developed apparently without anti-Rh hemolysins. Anti-D antibody can be produced artificially in rabbits and some other animals by injection of Rhesus blood or human D-positive blood, but Rh antibodies other than anti-D have not been produced in animals.

but were invariably in low titer. Hemolytic transfusion reactions have not been reported as the result of sensitization to the Lutheran antigen, nor has it been found responsible for any cases of erythroblastosis fetalis.

Summary of the Blood-Group Antigens

Seven different, genetically unrelated and immunologically distinct blood-group systems have been well established in human beings. Other antigens have been identified by occasional serums without sufficient study being possible for definite characterization, because of lowness of titer of the antibody, or rarity of the antigen. Many more, undoubtedly, are waiting to be identified. Of all the antigens described, only A, B and D are of enough clinical importance to warrant routine procedures concerning them — A and B because natural antibodies are universal in human beings lacking the antigens in their red cells, and D because of its considerable antigenicity and the consequent danger of transfusion reactions or erythroblastosis fetalis, or both, when D-negative persons are exposed to D-positive blood.

(To be concluded)

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Correction In the article by Drs. Robert S. Schwab and William R. Tillmann entitled "Artane in the Treatment of Parkinson's Disease," which appeared in the September 29 issue of the *Journal*, the sentence beginning "The effect of other antihistaminic drugs" on page 485, immediately before the summary, should be changed to read "The effect of other antihistaminic drugs, such as Thephorin, aminophylline and Benadryl mixtures and compounds (Dramamine), is in the process of evaluation."

cold agglutinin Immune anti-P has been reported, but is very rare The P antigen is therefore of almost no clinical importance Potent anti-P typing serum has occasionally been obtained from animals,

TABLE 6 The P System

PHENOTYPE	OBSERVED FREQUENCY IN UNITED STATES*	GENOTYPE	CALCULATED FREQUENCY %	REACTIONS WITH TYPING SERUM anti P
P-positive	71.4	P/P	21.6	+
		P/p	49.8	+
P-negative	28.6	p/p	28.6	0

*Based on data of Sanger¹¹ on 140 Harvard Medical School students and Children's Hospital personnel (1948)

but is not generally available Most anti-P serums are more active at 4°C than at higher temperatures

The Le (Lewis) System

The antigen Le^a was originally described by Mourant^{29, 30} and called "Lewis" Andresen,³⁰ in an independent publication, picked the letter L Andresen also identified Le^b, as a mendelian allele of Le^a, by means of a human serum antibody discovered in his laboratory Mourant's original "anti-Lewis" (anti-Le^a) agglutinated only the cells of homozygotes (Le^aLe^a), about 20 per cent of the population Anti-Le^b agglutinates about 80 per cent of all cells, missing all those positive with the original "anti-Lewis" (anti-Le^a) A few persons are negative to both anti-Le^a and anti-Le^b, in-

TABLE 7 The Le ("Lewis") System

PHENOTYPE	OBSERVED FREQUENCY IN UNITED STATES*	GENOTYPE†	REACTIONS WITH TYPING SERUM
	%		anti-Le ^a (anti Le ^a) anti Le ^b
{ "Lewis"-positive Le (a+b-)	20.5	Le ^a /Le ^a	+ 0
{ "Lewis"-negative, Le (a-b+)	79.5	Le ^a /Le ^b Le ^b /Le ^b	0† + 0‡ 0‡

*Data of Sanger (Cited by Race et al²⁹) on 132 Harvard medical students and Children's Hospital personnel

†Le^a = "Lewis" (Mourant) = L₁ (Andresen) Le^b = L₂ (Andresen)

‡Available anti-Le^a serums fail to agglutinate cells of heterozygotes therefore Le^a positive cells are probably homozygous.

§Approximately 5 per cent, in a limited series

dicating the probable existence of a third, fairly common allele at this locus Anti-Le^a, and anti-Le^b serums that we have seen have been more active at cooler temperatures (4 to 20°C) So far, no clinical problems have arisen with respect to the Lewis antigens Most, if not all, of the anti-Lewis antibodies so far identified have apparently been natural agglutinins (Table 7)

The K ("Kell") System³¹

An antibody active against the red cells of about 11 per cent of the population was first described in England in 1946 This antibody was found in the serum of a woman who had given birth to a baby with erythroblastosis fetalis The antigen identified by this antibody was named "Kell" from the name of the woman in whose serum it was found Since the first example in England, a fairly large

TABLE 8 The K ("Kell") System

PHENOTYPE	OBSERVED FREQUENCY %	GENOTYPE	CALCULATED FREQUENCY*	REACTIONS WITH TYPING SERUM
KK	10.17†	K/K	0.27	anti-K anti-k*
Kk	99.8*	K/k	9.90	+ +
kk		k/k	89.83	0 +

*Data of Levine et al³² (Anti-k = anti Cellano)

†Data of Sanger et al³¹

number of other examples of this antibody have been found in this country and abroad Anti-Kell has been formed in a Kell-negative person by injection of Kell-positive blood Some of the examples of anti-Kell serums so far identified have been hyperimmune blocking antibodies, comparable to anti-D The Kell antigen is thus of some clinical importance A new antibody, identifying the allele of the Kell factor, has recently been described by Levine et al³² and called "anti-Cellano" (Table 8)

The Lu ("Lutheran") System

Antibodies identifying a seventh unrelated blood group system (Table 9) were first found by Callender

TABLE 9 Lu ("Lutheran") System

PHENOTYPE	OBSERVED FREQUENCY IN ENGLAND*	GENOTYPE	CALCULATED FREQUENCY	REACTIONS WITH TYPING SERUM
	%		%	anti-Lutheran (anti Lu ^a)
Lutheran-positive Lu (a+)	8.0	Lu ^a /Lu ^a Lu ^a /Lu ^b	0.2 7.8	+ +
Lutheran negative Lu (a-)	92.0	Lu ^b /Lu ^b	92.0	0

*Data of Callender and Race¹⁸ on 582 English bloods

and Race¹⁸ in England About 8 per cent of red cells of Britishers are agglutinated by anti-Lutheran (anti-Lu^a) Anti-Lutheran has been found in the serum of Lutheran-negative recipients deliberately transfused with Lutheran-positive blood³³ The antibodies were active in saline solution at 37°C

a diagnosis. The rather short duration and rapid progress of the symptoms favor this diagnosis over some of the others, and this would be my first choice. Furthermore, by the law of averages I favor a malignant tumor. In my experience most of these tumors have been left-sided, so I would guess a left-sided tumor.

The second possibility I would consider is hyperplasia of the reticular cells of the adrenal cortex. This is a very interesting condition. It occurs mostly in females, and there is often a family history in the siblings. The typical story in females is usually as follows: together with certain characteristic changes in the external genitalia, the child is born with a large clitoris, she grows normally for the first one to eight years, she then develops axillary and pubic hair and grows rapidly, which suggests that androgen is being produced in excess somewhere in the body, finally, because of early epiphyseal union secondary to the excess of androgen, she stops growing at an early age. The net result is that her final height is about normal.

The reticular cells of the adrenal cortex have an interesting life history as worked out by the great Dr Sam S. Blackman, Jr.¹ The fetal reticular zone is well developed and apparently functioning, in the first two weeks of postnatal life it retrogresses but leaves behind some cells that give origin to the postnatal reticular zone, these cells lie dormant until about puberty, when they again show signs of activity and produce reddish-brown granules.

The life history of the reticular zone in cases with hyperplasia of the reticular cells is modified. In the first place the fetal reticular zone is increased, in the second place the cells that give rise to the adult reticular zone lie dormant only one to eight years, rather than up to the usual time of puberty.

We are now in a position to interpret the clinical manifestations. The anatomic changes at birth are undoubtedly the result of increased androgen production by the hyperplastic fetal reticular zone, the failure of axillary and pubic hair to develop in the first few months is due to the latent period when the fetal reticular cells lie dormant, finally, the rapid growth of axillary and pubic hair and of the external genitalia, if it does occur, is evidence of the recrudescence of the reticular cells.

The reticular-cell hyperplasia not only is much less frequent in the male but also runs a somewhat different course. It is very apt to be associated with Addison's disease, because of the encroachment of the reticular cells on the other layers of the adrenal cortex.

Against the diagnosis of hyperplasia in this particular case are the failure of the genitalia to be enlarged at birth and the absence of any clinical or laboratory findings suggesting Addison's disease (for example, the serum electrolyte values and electrolysate values for sweat). On the other hand the onset of pubic hair and of rapid growth at six years

of age is about the right time one would expect if this were the diagnosis. Furthermore, there must be cases in the male in which the activity of the fetal reticular zone is not sufficient to cause noticeable enlargement of the male genitalia. Finally, there must be male patients who do not have Addison's disease. Adrenocortical hyperplasia is my second choice.

I will now turn to possible disorders of the Leydig cells. First, a word about testicular function: the hypothalamus, by way of a neurohumeral pathway, stimulates the anterior pituitary body to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones, in turn, stimulate the testes, FSH leading to tubular development and LH controlling production of testosterone by the Leydig cell.

The first possibility we might consider here as a cause of increase in androgen production is a tumor of the Leydig cells themselves. This is very rare. No such tumor was felt. In the only case I know of with this diagnosis, the 17-ketosteroid excretion was over 1000 mg as compared with 66 mg per 24 hours in this case. I think we can dismiss this diagnosis as possible but unlikely.

One might consider a tumor of the pituitary body giving off too much LH. Such a diagnosis would seem reasonable, but I never heard of a pituitary tumor that did this.

The next possibility to consider is a disturbance in the hypothalamus, releasing FSH and LH and stimulating all functions of the testes. One meets this condition in the so-called "pineal syndrome." It is initiated, not by the hormone of the pineal body, but by any tumor in the region of the pineal body. Against such a diagnosis in the case at hand is the failure of the testes to be enlarged. The size of the testes is dependent almost entirely on the size of the tubules, and in the pineal syndrome development of the tubular, as well as the Leydig cells, occurs. There are no findings to suggest an intracranial lesion, and I think we can dismiss this diagnosis.

Finally, one comes down to the possibility of a selective overproduction of LH without FSH. This might cause stimulation of Leydig cells without stimulation of tubules. I had never heard of such a syndrome until recently when Dr Nathan Talbot mentioned it. I leave this for him to discuss. Such a diagnosis would seem to be compatible with the findings in this case, and I might put it down as a third choice.

It is now the vogue to divide adrenocortical hormones into three functional types, one for each layer of the gland. The innermost reticular layer is thought to produce the gluconeogenic, "sugar" or "S" hormone, the outermost glomerulosa layer is thought to produce the salt and water, sodium or "Na" hormone. It may be of interest to see what evidence there is for overproduction of each

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35481

PRESENTATION OF CASE

A six-and-one-half-year-old boy was admitted to the hospital because of rapid weight gain, growth of pubic hair and enlargement of the penis.

On routine examination nine months before admission, he had been found in good health, with normal development, weighing 44 pounds. The blood pressure was 100 systolic, 60 diastolic. The genitalia were noted as normal. Approximately six months before admission, however, he began to gain weight rapidly and to develop pubic hair and penile enlargement. He was otherwise completely asymptomatic and had been very energetic and active, with good muscular strength. He had a good appetite without special preferences, although he ate a great deal of meat and potatoes. There was no special craving for salt or sugar. There were no voice changes, development of axillary hair, acne or other skin changes.

The past history revealed that he was born in breech presentation at term and weighed 6 pounds, 10 ounces. Weight gain and development were normal.

A review of the systems was negative except for an episode of "abscessed ears" and tonsillectomy eighteen months previously for frequent upper respiratory infections. He rarely wet the bed, and there were no other genitourinary symptoms.

Physical examination showed a well developed boy. The weight was 65½ pounds, and the height 46 inches. He seemed very plump, with prominent abdomen and hips. The neck and cheeks were fat. Examination of the head, neck and chest was negative. The heart was slightly enlarged to the left. The rate was normal, and there was a Grade II pulmonic systolic murmur. An electrocardiogram gave a normal tracing. The abdomen was plump and full, but no masses were palpable. There was

definite, kinky pubic hair. The penis measured 7.6 cm in length and 6.3 cm in circumference. The testes were small and measured 1.9 cm in cross section. The skin was clear, and there was no acne or unusual pigmentation. There was no axillary hair. Neurologic examination was negative.

The temperature was 99.2°F, the pulse 100, and the respirations 22. The blood pressure was 132 systolic, 96 diastolic.

The urine had a specific gravity of 1.022. The tests for sugar and bile were negative. There were rare red cells and white cells in the sediment. The blood hemoglobin was 14 gm, and the white-cell count 7700, with 78 per cent neutrophils, 14 per cent lymphocytes and 8 per cent monocytes. The eosinophil count was 112 cells per cubic millimeter. The serum chloride was 106 milliequiv, the sodium 140.4 milliequiv, the carbon dioxide 25.5 milliequiv and the potassium 3.9 milliequiv per liter. The nonprotein nitrogen was 17 mg, and the fasting blood sugar 86 mg per 100 cc (the blood sugar of a specimen taken two hours after breakfast was 97 mg). A sample of sweat contained less chloride and more potassium per liter than normal. The urinary 11-17 oxycorticosteroid was 0.2 mg per 24 hours. The 17-ketosteroids were 6.6 mg per 24 hours.

X-ray films of the right hand and wrist indicated a bone age of seven years. Films of the skull failed to show any significant changes; the bones were of normal texture and density. The pituitary fossa was intact. Chest films showed clear lung fields. The heart was at the upper limit of normal size. The aorta was prominent. Anterior and posterior views of the abdomen showed normal appearance of the left kidney, spleen and liver. The right kidney was obscured by intestinal contents. There was no evidence of abdominal tumor.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FULLER ALBRIGHT* This seems like a straightforward case, but one never knows in these exercises.

We know that this patient was producing too much androgen. The rapid somatic growth and the early development of the genitalia are evidence of this. Besides, the 17-ketosteroid excretion was 6.6 mg per 24 hours, which is very high for a child of this age (normal value, 0 mg). There are two tissues in the body that produce androgen: the reticular cells of the adrenal cortex and the Leydig cells of the testes. We therefore expect to find some disorder in one of these two tissues.

I will first discuss the reticular cells of the adrenal cortex. The first possibility I would consider is a tumor, benign or malignant, of the adrenal cortex. Everything in this case is compatible with such

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tered have been on the left side. Left-sidedness to me makes no sense so I am always equally suspicious of the right. This is the second right-sided tumor of our series. Left-sidedness is presumably a statistical fluke, and I suspect that with time and increased experience the left-sided predominance will also disappear.

Careful search was made at operation for evidence of malignant spread of the tumor. Grossly, the capsule of the tumor was unbroken. No invaded lymph nodes were encountered. The tumor was excised in toto.

The tumor was transected after removal at the operating table. On the gross examination I made a diagnosis of cancer because of the unevenness of consistence in one area and distortion of the stroma. These gross findings have been present in other malignant adrenocortical tumors and consistently absent in the small, apparently benign, tumors that have been resected from patients with Cushing's disease. My experience is too limited for me to be certain but I have a hunch that in such tumors the gross pathology is more reliable than the microscopical. I am therefore fearful of recurrence in spite of my negative search for lymph-node metastases.

DR TRACY B. MALLORY: The tumor was a well encapsulated nodule of quite variable color with many bright-orange-yellow spots in it, indicating



FIGURE 1

that in portions of the tumor considerable lipoids were present (Fig. 1). The microscopical section showed a very variable picture (Fig. 2). Cells could be found that corresponded to all the various layers of the adrenal cortex. There were numerous lipid-filled cells corresponding to the fascicular layer, and also many of the big rather homogeneous eosinophil cells that are found in the reticular layer. There was not a great deal of pigment in the cells in this case. The question comes up whether this tumor was benign or malignant. Encapsulation would be in favor of its being benign. In some parts of the tumor very atypical cells with giant multiple nuclei were found, which anywhere else in the body would certainly be evidence of a highly malignant tumor. Our experience in adrenal tumors has in-

dicated that marked cellular atypicality of this type may be present in tumors that run a benign course. I think it very probable that if these slides were shown to a group of pathologists they would split fifty-fifty as to whether it was benign or malignant. My impression is that the outlook is relatively

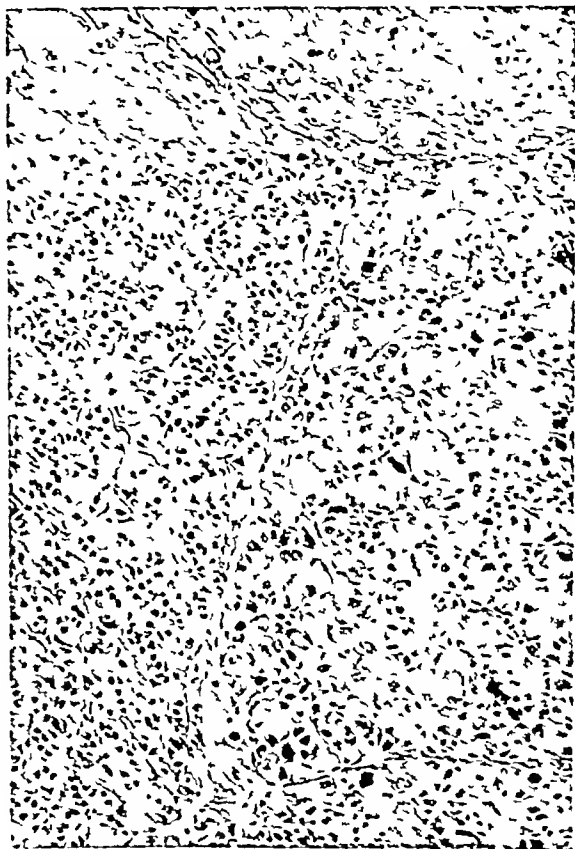


FIGURE 2

favorable although we did call it carcinoma. That may perfectly well be an error.

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CASE 35482

PRESENTATION OF CASE

A sixty-nine-year-old housewife was admitted to the hospital because of a "nervous breakdown." She had suffered from a chronic nonproductive cough most of her life, and nine months before admission, coincident with an emotional strain, her cough became worse and her appetite failed.

one of these hormones by the tumor that I have diagnosed. We have already discussed the androgenic hormone. Against overproduction of the glucocorticogenic hormone are the failure of the eosinophils to be decreased, the normal value for 11-17 corticosteroids and the rapid growth. In favor of some overproduction of the "Na" hormone is the hypertension and the low chloride and high potassium values in the sweat. It would seem, therefore, that this tumor was producing a large amount of androgenic hormone, a normal amount of the glucocorticogenic hormone and a slightly increased amount of the "Na" hormone.

DR NATHAN B TALBOT Our preoperative diagnosis was the same as that just given by Dr Albright. In the differential diagnosis the condition of greatest interest was a syndrome that we have now seen in a number of young boys. It is characterized by precocious masculinization, starting in early life. The testes are of normal size for age. The urinary 17-ketosteroid output is either normal or slightly elevated, and the urinary gonadotropin (FSH) assay is apt to be negative for 3 and 6 mouse units per 24 hours. Exploration of the adrenal glands of such patients fails to reveal either a tumor or bilateral hyperplasia. On the other hand, testicular biopsy reveals marked development of the interstitial cells of Leydig without more than minor evidences of testicular tubular development. It is believed that the precocity is due to a production of androgenic hormones by the Leydig cells and that these in turn have been precociously developed and activated by pituitary interstitial-cell-stimulating hormone (ICSH). It is further believed that the pituitary body has been activated to ICSH production by some sort of hypothalamic disturbance. Since most of these patients have shown no neurologic evidences of an intracranial lesion, it seems probable that the hypothalamic disturbance is of a functional nature rather than an organic, structural defect. Parenthetically, it may be added that the testicular interstitial cells occupy but a small volume, hence, it is possible for extensive interstitial-cell hyperplasia to occur without a clinically definite increase in gross testicular size. It is growth of spermatid tubules that accounts in the main for the increase in testicular size during adolescence.

So far as testicular size and masculine development were concerned, the patient under consideration corresponded to patients with the condition just described. On the other hand, he differed in the age at onset of precocity, which in his case was much too late for the above syndrome. He also differed in water and electrolyte status, for he had signs (questionable edema of the face, slight hypertension and cardiac enlargement) suggestive of a pathologic increase in the production of adrenocortical hormones of the type that cause sodium and water retention and potassium diuresis. To gain some objective information concerning the

present patient's adrenocortical "Na-K" hormone status, Dr William Locke applied a sweat electrolyte test on which he has been working recently. It might be interesting to hear the results of these studies.

DR WILLIAM LOCKE Methods for estimating the rate of secretion of the "Na-K" hormone are not so satisfactory as the methods for the other cortical hormones, as Dr Albright and Dr Talbot have said. In this case the hypertension may have indicated some overproduction of that hormone. The patient did not have hypochloremic alkalosis, which is sometimes associated with Cushing's syndrome and which has been attributed to an overproduction of the "Na-K" hormone in that condition. We have been studying variations in the electrolyte concentrations in sweat, with a view to using them as an index of "Na-K" hormone production. This subject was first studied by Dr J W Conn,² who showed that desoxycorticosterone acetate has somewhat the same effect on sweat as it has on urine composition—that is, it reduces the concentration of chloride and sodium, and increases the concentration of potassium. In this case the sweat chloride was 100 milliequiv, and the potassium 13.2 milliequiv per liter. Under the conditions of this test one would expect the chloride concentration in the sweat from a normal child to be perhaps three times what it was in this case and the potassium concentration to be approximately half what it was in this case. So we considered our findings to be suggestive evidence of an excessive production of the "Na-K" hormone.

CLINICAL DIAGNOSIS

Carcinoma of adrenal cortex

DR ALBRIGHT'S DIAGNOSIS

Carcinoma of adrenal cortex

ANATOMICAL DIAGNOSIS

Carcinoma of adrenal cortex

PATHOLOGICAL DISCUSSION

DR OLIVER COPE This patient had a tumor of the adrenal cortex. Why were the roentgenograms reported as showing no evidence of a tumor? The answer is that the tumor was small, not more than 3 cm in its greatest diameter and scarcely large enough to cast a shadow. The roentgenograms were excellently clear, and a shadow was present on either side just above the kidney consistent with that cast by the adrenal gland. The shadow on the right was denser than that on the left. In making the incision we anticipated that if a tumor were present it would be on the right side. This proved to be the case.

It is a curious thing, as Dr Albright has pointed out, that the overwhelming majority of the hyperfunctioning adrenocortical tumors we have encoun-

pelvis (Fig 1) A residue of barium was caught in a sigmoid diverticulum and in the appendix.

The patient was placed on complete bed rest, digitalized and given Hykinone, elixir of ferrous sulfate, 10 per cent hydrochloric acid and liberal supplements of vitamins with a salt-restricted diet. The temperature fluctuated between 100 and 101°F for the first seven days and then fell to normal (the weather was exceedingly warm during this period). After three days the pulse fell to normal limits.



FIGURE 1

Over the first three days she received 0.4 cc of Mercupurin in divided doses, with a 6-pound weight loss and slight relief of orthopnea. A total of 4000 cc of whole blood and the packed erythrocytes from 1500 cc were given during the first fifteen days. One transfusion was followed immediately by a febrile reaction, the temperature reaching 102°F. This subsided promptly without jaundice or hemoglobinuria. There was a steady rise in hemoglobin from 3.5 to 9.0 gm following the first seven transfusions. Three subsequent 500-cc transfusions in the ensuing four days failed to produce further elevation. A hematologic consultant was unable to determine the cause of the anemia, which he classified as normocytic and slightly hypochromic. As the blood count rose the cardiac status improved. There was subsidence of peripheral edema and great diminution in the pulmonary rales. No

cause for the wide variation in the blood non-protein nitrogen was established. On the twenty-first hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR W. PHILIP GIDDINGS* This history concerns an elderly woman with symptoms and signs suggesting disorder of nearly all the major body systems. Perhaps some of these are interrelated, and we can reduce the problem to simpler terms.

It is obvious that she was severely anemic, and the evidence all indicates a so-called secondary anemia. One immediately suspects chronic blood loss, but we are given no apparent source of bleeding. It is both regrettable and amazing that no stool examinations for occult blood are recorded.

After her anemia, the next apparent difficulty is that she was in cardiac failure. The suggestion by history of possible rheumatic fever at the age of twenty is not borne out by the electrocardiogram; at least she did not have evidence of rheumatic heart disease, nor was the murmur described suggestive of a specific lesion. With diuretics and correction of her anemia the cardiac status improved, and it is justifiable to conclude that her heart failure was largely if not wholly due to the anemia. At least that is my conclusion.

The next striking fact is that her renal function was impaired: she showed albumin, casts and red cells in the urine. The specific gravity did not rise above 1.013, phenolsulfonephthalein excretion was about half of normal, and she did not concentrate intravenous dye sufficiently for x-ray visualization of the upper urinary tract. All this bespeaks a diffuse renal lesion, which I take to have been independent of her other difficulties. I suppose she had a chronic glomerular nephritis, and shall ascribe the albumin and nonprotein nitrogen levels to this.

Let us now consider her liver. Here again we find evidence of functional impairment. The albumin-globulin ratio was decreased, bromsulfalein retention, alkaline phosphatase and prothrombin time were all elevated, though none of them to a very marked degree. Cephalin flocculation was ++ at forty-eight hours. Urinary urobilinogen and van den Bergh values were normal. In my limited knowledge of such matters, I should conclude that although a diligent search was made for evidence that some sort of biliary-tract disease underlay the clinical picture, the findings did not suggest a major hepatic disorder. I do not know whether or not her severe anemia, nephritis, cardiac failure and probable malnutrition could produce this picture in the liver, but I suspect that they might.

I should mention in passing her chronic cough. I see no cause for this in the history, physical examination or x-ray findings, except that its increased severity recently was due to pulmonary edema.

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A visit to her family doctor disclosed that she had lost weight and that her "blood was down to 70." She was given "iron pills," which, after a month, "raised her blood to 80." Six months before admission she noted the onset of weakness, increasing ease of fatigability, shortness of breath and increased anorexia. After two months she again consulted her doctor, who gave her ten injections of liver extract and prescribed liver pills, which she took religiously until the time of admission. No significant improvement in her symptoms followed this medication. One month before admission she first noted orthopnea, followed in two weeks by swelling of the ankles and legs. Constipation became troublesome at approximately the same time, and her stools became smaller in size. There was one brief episode of abdominal cramps, and it became necessary for her to take cathartics. Over the nine-month period there was progressive weight loss totaling 40 pounds. She had never experienced dysphagia, vomiting, hematemesis, melena, rectal bleeding or jaundice, and there had been no dysuria or gross hematuria.

At the age of twenty she suffered an attack of pneumonia complicated by "muscular and inflammatory rheumatism." The left breast was removed because of an "adenoma" thirty years previously. "Polyps" were removed intravaginally at thirty-five and sixty-nine years of age.

On physical examination the mucous membranes were generally pale. The tongue was red, with atrophy of the marginal papillae. The left breast had been removed by simple mastectomy. Tiny, firm, shotty lymph nodes were palpable in the left axilla. There was moderate kyphosis of the thoracic vertebra, and respiratory expansion was diminished. Breath sounds were distant, the percussion note was hyperresonant, and scattered coarse rales were heard over both pulmonary bases. At 30° elevation the neck veins became distended and pulsating. The heart was enlarged to the left, and there was a Grade II precordial murmur. A++ pitting edema of the lower extremities extended upward to the knees. A large, hard, smooth mass was palpable in the right lower quadrant of the abdomen extending downward into the pelvis. One examiner believed that he could outline the lower border of the lesion by dipping the palpating fingers into the pelvis. The lesion was movable to palpation but unaffected by respiration. The liver and spleen could not be felt. On rectal examination there was palpable fullness in the right posterior quadrant, but a rectal shelf was not encountered. Vaginal examination was not completely satisfactory, and the uterine fundus was not outlined.

The temperature was 102°F, the pulse 100, and the respirations 20. The blood pressure was 110 systolic, 60 diastolic.

Examination of the blood showed a red-cell count of 1,160,000, with a hemoglobin of 3.5 gm, and a

white-cell count of 9000, with a normal differential ratio but with 8 metamyelocytes and normal appearing platelets. The erythrocytes were hypochromic. No normoblasts were seen. Except for continued hypochromia subsequent blood smears were not remarkable. The hematocrit reading was 20 per cent. Reticulocyte counts were 0.6 per cent and 0.4 per cent respectively. A sternal-marrow aspiration was reported as not remarkable. Repeated urinalyses were consistently acid, with specific gravities between 1.008 and 1.013. Albumin varied from a trace to ++. The sediment contained 4 or 5 white blood cells per high-power field and 2 or 3 red blood cells per high-power field on one occasion. Occasional granular casts were seen. Twelve-hour urine concentration studies yielded a specific gravity of 1.012. The phenolsulfonephthalein excretion was 34 per cent in two hours. A urine culture grew a few colonies of colon bacilli. The total serum protein varied from 6.18 to 7.19 gm per 100 cc, the albumin from 3.23 to 3.35 gm, and the globulin from 2.95 to 3.84 gm. Four successive nonprotein nitrogen determinations gave readings of 31, 68, 30 and 68 mg per 100 cc. Successive prothrombin determinations were 52, 44, 57, 48 and 70 per cent of normal. A van den Bergh reaction was less than 0.4 mg per 100 cc on direct and indirect tests on one occasion, and 0.2 mg direct, 0.4 mg indirect, on another. The alkaline phosphatase varied between 20.1 and 16.9 units per 100 cc. The cephalin-flocculation test was + at twenty-four and ++ at forty-eight hours. Urinary urobilinogen examinations were 0.25 and 0.29 Ehrlich units respectively. Bromsulfalein excretion studies showed 14.2 per cent retention of the dye in forty-five minutes.

A cytologic examination of smeared vaginal secretions was negative. An electrocardiogram was within normal limits. A barium enema showed lateral and upward displacement of the cecum, ascending colon and proximal transverse colon by a large, smooth mass lying in the right lower quadrant. The deformity was that of a pressure defect, with no evidence of involvement of the wall of the colon.

A chest x-ray examination revealed increased linear markings throughout both lung fields. The heart was slightly enlarged in the region of the left ventricle. The aorta was moderately tortuous and calcified in the region of the arch.

Films of the skull and lumbar spine were negative for evidence of metastases.

In an intravenous pyelogram there was an insufficient amount of opaque material on either side to warrant adequate visualization of the urinary passages. The right kidney could not be traced. The left seemed lower than usual but within normal limits. There was an impression of a rounded, soft-tissue mass occupying the right side of the

is one of the first places to look in searching for the cause of an obscure secondary anemia (The next is the stomach) So far as I know, the precise reason for the anemia is not known

In spite of the x-ray findings, I am constrained to make a diagnosis of carcinoma of the cecum. It fits the picture too well for me to consider any other. An obvious diagnosis to consider is metastasis to the peritoneal cavity from a carcinoma of the breast removed thirty years previously. I see no way to support such a diagnosis. The question arises whether or not her liver difficulties could have been due to metastatic disease. Although cancer of the right colon typically metastasizes late, this was a large tumor and could well have spread through the portal system. I am certain that we cannot answer this question definitely, but I should not be surprised to learn that she had liver metastases.

I do not know whether an intramural tumor of the wall of the bowel at this level, such as a neurofibroma, would give this picture. It does not look at all like a lipoma. Neurofibrosarcoma would produce the same effect in the way of anemia as the classic carcinoma of the bowel, but I do not know whether or not it would still leave the mucosal pattern intact. I am going to guess that she had a primary neoplasm of the right colon of some sort.

DR WYMAN: From the x-ray standpoint I do not think it is tenable to place the primary tumor especially carcinoma, in the right colon. I wonder if Dr Giddings would consider a papillary cystadenoma or cystadenocarcinoma of the ovary?

DR GIDDINGS: It is conceivable that the mass is a little lower in the film than I judged it to be from the physical examination as recorded. Ovarian tumors are usually capable of being bimanually palpable.

DR WYMAN: We have seen them as high as and higher than this in many cases.

DR DANIEL S. ELLIS: Are the x-ray findings consistent with a dermoid cyst?

DR WYMAN: It should be of less density because it contains fat. This seems to be of increased density.

CLINICAL DIAGNOSIS

Carcinoma of ovary

DR GIDDINGS'S DIAGNOSES

Tumor of cecum

Secondary anemia

Cardiac failure

Chronic glomerular nephritis

Metastases to liver?

ANATOMICAL DIAGNOSIS

Renal-cell carcinoma of right kidney

PATHOLOGICAL DISCUSSION

DR SOMERS STURGIS: This woman looked older than her stated age, and she was moribund on admission. When the service first saw her she was desperately sick, and it was very questionable in their minds whether they could ever get her in shape for surgery. The gynecologic service favored an ovarian lesion and rather suspected that she had a diffuse carcinomatosis to account for the anemia and lack of much guaiac in the stool. It was on that basis and with that diagnosis in mind that she was operated on.

The laparotomy was done, and a large, smooth, nonadherent, encapsulated tumor was found retroperitoneally, lying behind the ascending colon. The pelvis was normal. The uterus was small, and both ovaries were atrophic. It was obvious that this was a renal neoplasm. It was dissected off without difficulty from the ascending colon.

DR MALLORY: The resected specimen was an enlarged kidney, enlargement being due to a characteristic renal-cell carcinoma, which had not invaded the renal pelvis. This explains why there had not been, at any time, hematuria. The tumor had not extended into the renal vein as they so often do. The patient made a good operative recovery and left the hospital comparatively well.

We shall pass it over — possibly unwisely — as an unexplained and irrelevant matter

We now come to the crux of the story, the mass in the right lower quadrant of the abdomen. This was probably a surgical lesion and is the reason for my having been assigned this case. I must confess, with apologies to my medical colleagues, that now for the first time I feel on familiar ground.

The tumor was large, smooth and hard. We immediately think of the cecum, kidney, liver, gall bladder and ovary as possible origins of such a mass. That it was not inflammatory is evidenced by its mobility, implied lack of tenderness, normal leukocyte count and absence of sustained fever. Nonmalignant hard tumors are unusual unless calcified, which is the reason that I suspect this was cancer.

Was it ovarian? One observer demonstrated it to be out of the pelvis, and it was not definitely palpable on vaginal examination. I do not think it was in the ovary. The physical examination and x-ray films do not agree with the behavior of hepatic or cholecystic tumors, and I believe we can rule out the liver and gall bladder. Nor could it have been kidney: a movable renal mass would have descended with respiration, and this did not.

In a patient with anemia of this degree and a mass at the right lower quadrant, one would like to know the guaiac reaction on the stool.

DR TRACY B. MALLORY: Three specimens were examined: one was negative, one was +, and one was + or —.

DR GIDDINGS: I might say, it is rather surprising that a retrograde pyelogram was not done, since the mass in the right lower quadrant was sufficient in size to displace the major viscera. One would think the surgeon would want to know the precise relation of the ureter to the mass, but I gather that the investigation there was not done. I would also question once and for all whether this could have been a renal tumor. I do not think it was.

That leaves us with the cecum, unless we consider such rarities as mesenteric tumors. This would be a good time to see the x-ray films.

DR STANLEY M. WYMAN: The chest film taken in the supine position is that of an elderly woman with an enlarged heart, apparently chiefly left ventricular, with a tortuous arteriosclerotic aorta. The lung fields, themselves, reveal no definite active localized disease, but there does appear to

be considerable emphysema, as shown by increased anteroposterior diameter of the chest. The films from the barium enema demonstrate quite conclusively a large mass lying in the right lower abdomen over the sacrum, lumbar spine and iliac crest (Fig. 1). This displaces the right colon as described. The pressure is chiefly on the ascending colon, and to a lesser degree on the cecum and on the hepatic flexure. There is no evidence of intrinsic involvement although the mass may be adherent to the colon. The cecum itself is quite well seen in this film and lies lower and more medially than usual, in keeping with the pressure from the mass. There is a definite area of dense calcification seen in the right midabdomen, better seen on several other films. This does appear to be important and is not consistent with a calcified lymph node.

DR GIDDINGS: Could it be a vessel?

DR WYMAN: I do not believe so. The patient does have tortuous arteriosclerotic vessels in the pelvis, and probably higher up than I can demonstrate in the aorta. There is some calcification to the left of the spine — possibly, in the splenic artery. The mass is better seen in films of the attempted pyelogram. It lies below the right kidney. The kidney on the right is not outlined, but what seems to be its lower pole is not grossly remarkable. The left kidney is definitely small, measuring perhaps a quarter of the usual size. The calcification is present in all these films, and it occupies essentially the same position. To me, that is one of the more interesting features of these films.

DR ALFRED E. KRANES: How about the visualized bones? Do they show any changes of metastatic involvement?

DR WYMAN: They seem diffusely osteoporotic, in keeping with the patient's age. I do not see any gross metastases, but we know that with osteoporosis we can miss extensive metastases with great facility.

DR GIDDINGS: That does not make me feel any better. I am at a loss to explain the calcification here. It was not mentioned before.

Of course, the diagnosis that immediately suggested itself to me was carcinoma of the cecum. This is a classically insidious tumor that frequently grows to large size before its detection. One of its most characteristic features is an accompanying severe anemia of the hypochromic variety. As Alvarez and others have pointed out, the cecum

The Autocrat of the Breakfast Table would also have enjoyed reading Luyk's lucid exposition of his subject, "Progress without Statistics." In the judgment of the *Journal* his analysis is adequate.

INDUSTRIAL MEDICINE — A NEW PROGRAM

A BLUEPRINT for the expansion and improvement of industrial medicine in Massachusetts will be offered on December 14 at 2:00 p.m. at the Hotel Statler, in Boston, by the Committee on Industrial Health of the Massachusetts Medical Society. This venture is a logical outgrowth of the Massachusetts Health Conference in February, on which occasion it became evident that a fresh outlook and a renewed effort were needed. The interest was present, but the initiative seemed then to be lacking.

Since that meeting the Committee on Industrial Health has been reorganized with new and enthusiastic membership, and a section on industrial health has been established in the Society. It is under such auspices that the program of December 14, published elsewhere in this issue of the *Journal*, will be presented.

Massachusetts is a highly industrialized state in which many physicians who devote their full time to the medicine of industry have done excellent work, and in which many others, engaged in part-time activities, have discharged their functions with varying degrees of competence and effectiveness.

The actual practice of industrial medicine is, fortunately, an area in which there can be little real conflict between labor and management. Management, when properly informed, is as eager to improve existing programs or institute new ones for the health and safety of workers as labor is to cooperate in attaining the same high objectives. The physician, as the working agent, is equally respected by both sides.

In this effort to bring together representatives from management, labor, industrial nursing and industrial medicine to discuss common problems and work out effective solutions, the interest of all physicians is sought.

INFECTIONS WITH THE "COXSACKIE VIRUS"

THE discovery by Dalldorf and Sickles^{1,2} of a new virus from human cases resembling poliomyelitis and the subsequent isolation of this virus by Melnick, Shaw and Curnen³ from cases that were diagnosed as nonparalytic poliomyelitis, aseptic meningitis or fever of unknown origin were recently reviewed in these columns.⁴ The latter workers found the new virus to be widespread in this country during the summer of 1948. Certain new and significant observations have been added by the original discoverers^{5,6} and deserve mention in view of the interest stimulated by their work and because of the extensive epidemics of poliomyelitis that have occurred in and around Boston during the past summer.

The new virus was originally isolated by the Albany workers from 2 young boys who suffered from what was believed to be paralytic poliomyelitis during August, 1947. The authors usually referred to it as the "suckling mouse virus" because it was originally isolated by intracerebral inoculation of mice three to seven days old. They have now chosen to call it the "Coxsackie virus" after the village in upstate New York where the first human cases were recognized.⁶

Dalldorf⁵ later isolated his virus from 5 out of 21 fecal specimens collected during a rather large epidemic of poliomyelitis that occurred in 1947 in Wilmington, Delaware. This epidemic was noteworthy because other investigators had failed to isolate the classic poliomyelitis virus from the patients, so that the new virus was considered as probably causally related to some of these cases. Some of the clinicians and epidemiologists who investigated this outbreak considered the disease to be atypical in two respects: the unusually large number of multiple cases in families and the transient nature of the paralysis in many patients.

Additional studies were carried out by the Albany workers during 1948 in the course of which they isolated the new virus from 10 out of about 130 specimens collected from "poliomyelitis" patients in upstate New York.⁵ These isolations were from widely scattered outbreaks and from isolated cases,

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OLIVER WENDELL HOLMES AND BIOSTATISTICS

A CENTURY ago when a patient died from puerperal infection, the physician (and doubtless the patient) was considered merely unlucky. Holmes, however, was not content to stomach this kind of ill luck. He gathered the facts, quantitated them and proved statistically that the doctor was more than unlucky. He was a "pestilence carrier (who) must look to God for pardon for man will never forgive him."

Holmes "had the chances calculated that a given practitioner shall have sixteen fatal cases in a month." By comparing this "unlucky" series of sixteen births with the total number of births in the community not complicated by infection, he found that "there was not one chance in a million

million millions that such a series should be noted" as a purely fortuitous phenomenon.

During the intervening hundred years, while the controversial aspects of puerperal sepsis were being settled, the mathematicians have been busy, first with whittled pencils and then with slide rules and calculating machines perfecting modern biostatistics. It is not necessary to wait for odds of a billion billion to one in order to demonstrate the significance of an observation, and the textbook on biostatistics is today part of the research-minded physician's vade mecum, whether he likes it or no.

The "or no" reaction, however, is so common as to be almost instinctive among the majority of physicians, who have no occasion to use the binomial theorem when computing doses of sulfadiazine or cutting for the stone. To those who enjoy a kind of statisticophobia, who nevertheless are compelled by the inner spirit of curiosity and research to study a series of operations, autopsies, blood counts, x-ray examinations or whatnot in order to find the solution to some challenging medical problem, a recent progress report by Luykx* will be found worthy of thoughtful reading. The purpose of Luykx's contribution is to give "the reader of medical and scientific literature, the medical 'common man'" an appreciation of the need for, and the purposes of, proper presentation and analysis. "The student of medicine must have some knowledge of technics of handling quantitative data (1) in order to understand a correct presentation and (2) in order to form a judgment as to whether a given exposition or analysis is adequate or not."

Although electric calculators have made Einsteins of office secretaries, Luykx makes it abundantly clear that there is more to a formula than grinding it through the machine. Practicing physicians will be cheered by the statement

The technic of calculating the mean and standard deviation will not be discussed here. This is a matter of the proper use of a calculating machine or a slide rule. Much more important is a correct understanding of the meaning of these parameters.

*Luykx, H. M. C. Progress without statistics. Council on Pharmacy and Chemistry. *J. A. M. A.* 141:195-201, 1949.

and the studies show that the agent was widely disseminated in New York State during that summer. Furthermore, at least one antigenically distinct strain and possibly others identified differ in the nature of the disease they produce in mice.

The earlier strains were incapable of infecting monkeys and had the unique property of causing disease only in very young mice and hamsters although this may later be modified experimentally. In mice they caused lesions of the muscles rather than of the central nervous system. They were thus distinct from the classic monkey-pathogenic poliomyelitis virus, which produces central-nervous-system lesions in monkeys and shows no antigenic relation to the new virus. Certain of the new strains, however, appear to produce lesions in both the muscles and the central nervous system. Thus far, even these new strains have failed to cause lesions that resemble those of poliomyelitis.

Pathological studies of patients have, to date, been quite limited because the only fatal cases have apparently been caused by classic strains of poliomyelitis virus. This leads one to suspect that the new agent is less malignant for human beings than the monkey-pathogenic strains. Studies in the experimental disease have also indicated that the serologic diagnosis of infections with the new agent may be quite difficult.

In the mice the outstanding lesion has been the destruction of muscle that becomes a rich source of virus. The muscle degeneration suggested the possibility that studies of creatine and potassium balance might be used as a diagnostic aid. Infected mice were found to develop quite rapidly a marked creatinuria coincident with a loss of muscle potassium and creatinine.⁶ It was therefore suggested that similar studies might be useful in human cases.⁵

In discussing these findings, Gifford and Dalldorf⁶ cite reports from the literature of creatinuria following paralytic poliomyelitis. The muscle findings in reported cases of poliomyelitis, however, have been variable and obviously require re-examination in the light of the more recent findings in experimental infections with the Cocksackie virus. Furthermore, the reports of cases of poliomyelitis in which muscle groups that apparently were totally

paralyzed have rapidly and completely recovered; their function likewise require re-evaluation. It is hoped that future observers will have available more extensive studies of muscles from cases of suspected poliomyelitis, with and without paralysis. It is necessary to determine whether the muscle lesions caused by the classic poliomyelitis virus and by the new viruses have distinctive clinical and histologic features and also what the pathogenic potentialities of these tissues may be. This is particularly important in view of the finding of central-nervous-system lesions produced by some of the new strains.

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HEAT VERSUS VIGOR

THE importance of temperature as perhaps the leading environmental factor determining the success of man's attempts at life on this planet is stressed by Mills,* writing for *Science*. His analytic essay, emanating from the Laboratory for Experimental Medicine of the University of Cincinnati, suggests that it's not so much the humidity that counts as it is the heat — although the humidity also plays its part.

If the animal body is considered somewhat in the light of an internal combustion engine, the working efficiency of men, horses and dogs ranges between 20 and 25 per cent, and even this degree of efficiency depends on the rapid dissipation of its waste heat. Diesel did better, having achieved a working efficiency of 40 per cent for his well known engine.

In view of such a summer as New England and other parts of the world have recently experienced, it is easy to agree with Mills that the lowered com-

*Mills, C. A. Temperature dominance over human life. *Science* 110 267-271 1949.

from fundamental contributions of various authors are appended to the various chapters, which also include extensive bibliographies. For the literature previous to 1920, the reader is referred to Vol. II of the *Handbuch der speziellen pathologischen Anatomie und Histologie, Jage*, Berlin, 1928-1937. The book is well published but sparsely illustrated for its type. It should be in the reference collections of all medical libraries and available to ophthalmologists.

Foundamentals of Internal Medicine. By Wallace M. Yater, M.D., M.S. (in Med.), director Yater Clinic, Washington, D.C. Third edition. 8°, cloth, 1451 pp., with 315 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1949. \$12.00.

This new edition of a standard treatise has been thoroughly revised and brought up to date. Eighteen collaborators have written certain chapters of the text. A new and enlarged article on electrocardiography has been included. Sections on chemotherapy and therapy with antibiotics and on inhalation therapy have been added. The drug dosage has been given in the metric system and the old apothecary system discarded. A comprehensive index concludes the text. The book is well published and should be in all medical libraries and available to the practicing physician.

International Digest of Health Legislation. Vol. I No. I, 1948. 8°, paper 144 pp. Geneva, Switzerland: World Health Organization, 1948.

This new periodical succeeds the first section of the *Bulletin mensuel de l'Office International d'Hygiène Publique*, which ceased publication in December, 1946. It comprises the orders, decrees and regulations for the governments in the World Health Organization. It is published in two languages, English and French, and issued as separate or bound numbers. This is the English edition in bound form.

Diseases of the Liver, Gallbladder and Bile Ducts. By S. S. Lachman, M.D., assistant professor of clinical medicine, Cornell University Medical College, assistant attending physician, New York Hospital, adjunct physician, Mt. Sinai Hospital, and assistant in postgraduate medical instruction, University Extension, Columbia University. Second edition. 8°, cloth, 1135 pp., with 147 illustrations and 2 color plates. Philadelphia: Lea and Febiger, 1949. \$18.00.

The text of this second edition of a standard work has been completely revised. The chapter on infectious hepatitis has been completely rewritten. Large bibliographies are appended to the various chapters. There is a comprehensive index. The book is well published and is recommended for all medical libraries and to all persons interested in the liver and its diseases.

Tumors of Bone. By Charles F. Geschickter, M.D., professor of pathology, Georgetown University School of Medicine, consultant in pathology, United States Naval Medical School, consultant in pathology, Mt. Alto Veterans' Administration Hospital, and pathologist-in-chief, Gallinger Municipal Hospital, Washington, D.C., and Murray M. Copeland, M.D., professor of oncology, Georgetown University School of Medicine, consultant in surgery, Gallinger Municipal Hospital, Washington, and special consultant, Federal Security Agency, Public Health Service, Cancer Control Branch, Washington. Third edition. 4°, cloth, 810 pp., with 642 illustrations. Philadelphia: J. B. Lippincott Company, 1949. \$17.50.

The previous editions of this standard treatise were published in 1931 and 1936. The third edition has been thoroughly revised, and the subject brought up to date. Chapters on fibrous dysplasia, osteoid osteoma, tumors of the spine, endocrine changes in bone and rare diseases of bone have been added. The chapters on embryology, chondroblastomas, and treatment of bone sarcoma have been entirely rewritten. The tabulations of bone tumors, on which the book is based, have been extended to include more than 500 additional cases. The illustrations have been revised by the addition of more than a hundred new ones and the deletion of a large number of the old ones, with the object of presenting the best possible reproductions of representative roentgenograms,

gross specimens and photomicrographs. Lists of selected references are appended to the various chapters. There is a good index. The publishing is well done, and the illustrations are excellent. The book, although justifiably expensive, should be in all medical libraries, and available to pathologists, orthopedists and surgeons.

The Temporal Bone and the Ear. By Theodore H. Bast, Ph.D., professor of anatomy, University of Wisconsin Medical School, and Barry J. Anson, Ph.D., professor of anatomy, Northwestern University Medical School. 8°, cloth 478 pp., with 165 illustrations. Springfield, Illinois: Charles C. Thomas, 1949. \$12.00.

This monograph presents a comprehensive study of the development and the adult anatomy of the ear and the temporal bone. Concerning the pathology of the ear only such information is given as relates to development. The text has been organized on a developmental basis, beginning with the otic labyrinth, after the first chapter on the general anatomy of the temporal bone and the ear. The following chapters discuss the periotic labyrinth, the otic capsule, histologic variations and pathologic processes, bone dysmorphies, the origin and development of the middle ear and related air spaces, and the auditory ossicles. The final chapter presents a historical survey of the structure and function of the internal ear, covering the period from 550 B.C. to the present. Bibliographies are appended to the various chapters. There are good indexes of authors and subjects. The book is well published, and the illustrations are excellent. Considering the large number of expensive figures and plates, the price of the book is not excessive. The volume should be in all medical libraries and in the libraries of otologists and anatomists.

Nutrition and Diet in Health and Disease. By James S. McLester, M.D., professor of medicine, University of Alabama School of Medicine. Fifth edition. 8°, cloth 800 pp. Philadelphia: W. B. Saunders Company, 1949. \$9.00.

This standard treatise was first published in 1927 and the last edition was printed in 1945. In this new edition much of the text has been rewritten, and the work now conforms to the knowledge gained during the war years. A section on folic acid has been added, and the material on the vitamins and their functions on deficiency diseases and on protein has been revised. The more liberal diet now used in peptic ulcer and the high-protein regimens used in cirrhosis and other diseases of the liver are discussed, data on the low-salt diet for congestive heart failure and the sodium-free diet for arterial hypertension have been added. New food tables have been included in the text. The chapters on the feeding of infants, by Dr. Philip Jeans, and on nutrition in industry, by Dr. Robert S. Goodhart, have been entirely rewritten. There is a new chapter on the feeding of surgical patients by Dr. Charles C. Lund, of Boston. There is a comprehensive index, and the book is well published in every way. The use of a lightweight paper has resulted in a book light in weight for its size. The volume should be in all medical libraries and should prove valuable to the practicing physician as a standard reference text.

A Primer of Electrocardiography. By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University School of Medicine, senior visiting physician, Chaney Hospital, consultant in cardiovascular diseases, Ochsner Clinic, and visiting physician, Touro Infirmary, New Orleans, and Travis Winsor, M.D., assistant clinical professor of medicine, University of Southern California School of Medicine, director of Nasb Cardiovascular Foundation, Hospital of the Good Samaritan, junior attending physician, Los Angeles County Hospital, and junior attending physician, Children's Hospital, Cardiac Department, Los Angeles. Second edition. 8°, cloth, 245 pp., with 265 illustrations. Philadelphia: Lea and Febiger, 1949. \$4.50.

This primer, intended for the beginner, has been revised in certain particulars. The bipolar precordial leads have been replaced by the unipolar leads, and it is recommended that they be employed exclusively with the standard leads in clinical electrocardiography. The book is well published, and the illustrations are excellent.

Dinner Meeting 6 p.m. Chairman, Arthur W. Allen, M.D., president, Massachusetts Medical Society

Remarks by Mr. Andrew B. Holmstrom, vice-president and general manager, Norton Company, Worcester, Massachusetts, Mr. Albert G. Clifton, legislative agent, Congress of Industrial Organizations, and Mr. Kenneth J. Kelley, secretary-treasurer and legislative agent, Massachusetts Federation of Labor "Rehabilitation of the Chest Patient" Dwight E. Harken, M.D., assistant clinical professor of surgery, Harvard Medical School, visiting thoracic surgeon, Boston City Hospital, and senior associate in thoracic surgery, Peter Bent Brigham Hospital

CORRESPONDENCE

A PHYSICIAN DISAGREES

To the Editor Fair-minded physicians who are members of the American Medical Association must feel ashamed of the official statement put out by the Board of Trustees of the Association in the October 15 issue of the *Journal*. In this statement the Trustees accuse the Department of Justice of the United States of waging a campaign to discredit American medicine and terrorize physicians into abandoning their opposition to compulsory health insurance. A careful perusal of the complete statement fails to show any concrete evidence to support this claim. A series of assumptions apparently forms the basis for this attack upon the integrity of the Justice Department of the United States.

In view of the past history of the American Medical Association and the evidence of persisting activities on the part of various groups in organized medicine, in violation of existing laws, to interfere with the development of plans to improve the delivery of medical care it seems that the Trustees are not in a very satisfactory position to try to besmirch the activities of the Department of Justice.

Actually, in 1938 the American Medical Association was convicted for breaking certain laws in the celebrated case of the Group Health Service in the District of Columbia, and this conviction was eventually upheld by the Supreme Court of the United States. In this instance it was the American Medical Association that was trying to discredit a group of physicians and to terrorize physicians from developing a plan to deliver medical care. Since then the Department of Justice has been receiving complaints from physicians and lay groups that similar tactics are being employed by organized medicine throughout the country. Investigation has provided enough evidence of disregard of the law by organized medicine to make the Department of Justice decide to bring suit in two instances. It seems only fitting in view of these facts that the Department should investigate further the numerous complaints that are made to it. To claim without evidence that such actions are aimed at terrorizing physicians rather than to compel them to obey the law seems quite unworthy of men honored by the medical profession to hold the high office of Trustees of the American Medical Association. I believe the national medical society should urge individual physicians and organized groups of physicians to obey the laws as they exist.

If any group does not believe in the existing laws it is fitting that attempts should be made through authorized methods to change them. The profession and the public should realize that there are thousands of reputable physicians who believe in the development of a national health program to be financed in part by compulsory health insurance such as President Truman favors.

CHANNING FROTHINGHAM, M.D.

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NOTE Further perusal of the statement issued by the Board of Trustees discloses the following paragraphs, relating to the alleged threatening of medical societies by Administration leaders: "On February 28, 1949, for example, one of the National press associations carried a dispatch from Washington quoting Government officials as stating that anti-trust actions would be started against 'several' medical societies soon after the Compulsory Health Insurance drive was started in Congress [italics ours]." — Ed

BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Food Poisoning By G. M. Dack, Ph.D., M.D., professor of bacteriology and director, Food Research Institute, University of Chicago School of Medicine. Revised edition. 8°, cloth, 184 pp., with 13 tables. Chicago: University of Chicago Press, 1949. \$3.75.

This second edition of a special work has been revised, and the subject brought up to date. The various chapters include chemical poisoning in food, poisonous plants and animals, botulism, staphylococcal food poisoning, salmonella, alpha type streptococci (*Streptococcus faecalis*) in relation to food poisoning, significance of other bacteria and infections to be differentiated from food poisoning. Lists of references are appended to the chapters. There are indexes of authors and subjects. The small book is well published and should be in all medical libraries.

Public Health in the World Today Edited by James S. Simmons, dean, Harvard School of Public Health, assistant editor, Irene M. Kinsey. With a foreword by James B. Conant, president of Harvard University. 8°, cloth, 332 pp. Cambridge, Massachusetts: Harvard University Press, 1949. \$5.00.

The papers presented in this volume were delivered during 1947-1948 at the public-health forums, conducted by the Harvard School of Public Health. Twenty-three eminent persons in their particular fields participated in the forums. The material is divided into various aspects of public health as follows: the profession of public health, public health in the United States today, public-health programs and problems abroad, and public health in a new era. The volume is excellently published but is marred by the lack of an index. It should be in all collections on the subject.

Natural Products Related to Phenanthrene By Louis F. Fieser and Mary Fieser, Department of Chemistry, Harvard University. Third edition of the monograph previously entitled *Chemistry of Natural Products Related to Phenanthrene*, by L. F. Fieser. 8°, cloth, 704 pp., illustrated. New York: Reinhold Publishing Corporation, 1949. \$10.00. (American Chemical Society Monograph No. 70.)

The authors have revised this standard reference book to bring it up to date. The first and second editions were published in 1936 and 1937. Despite its formidable title, the work is definitely of medical interest. Some of the chapters discuss the quinone and opium alkaloids, sterols and bile acids, sex hormones, adrenal cortical hormones, steroid metabolism and cardiac active principles. The pertinent literature is cited in footnotes on the appropriate pages. There are comprehensive indexes of authors and subjects. The printing is well done with a good type on light-weight paper, producing a volume light in weight for its size and yet conserving space. The volume is a good example of publishing in which some consideration is given the prospective reader. The book should be in all medical, physiologic and chemical libraries and in commercial laboratories.

Histology and Histopathology of the Eye and Its Adnexa By I. G. Sommers, M.D., assistant professor (ophthalmology), College of Medical Evangelists, and medical officer (E. E. N. T.) United States Public Health Service, Los Angeles, California. 8°, cloth, 784 pp., with 69 illustrations. New York: Grune and Stratton, 1949. \$12.00.

This new book is based on the lecture courses given by the author over many years to his students. The text is divided into three parts: normal histology, embryology and senescence, general pathology (in relation to the eye), and histopathology of the eye. Under the heading "Reading of Source Material," extensive lists of short pertinent excerpts

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TRANSFUSION TREATMENT OF SHOCK DUE TO MYOCARDIAL INFARCTION*

FRANKLIN H. EPSTEIN, M.D.,† AND ARNOLD S. REIMAN, M.D.†

BOSTON

THE pathogenesis and treatment of the vascular collapse often attending myocardial infarction have perplexed investigators for many years. Particularly vigorous in recent years has been the debate over the safety and efficacy of treatment with transfusions of blood or plasma. Although a few case reports of such treatment have appeared in the literature^{1, 2} and many opinions have been given pro^{3, 5} and con,⁶⁻⁸ no series of cases has yet been published.

At the New Haven Hospital transfusion of patients in shock after myocardial infarction has both advocates and opponents. During the past six years some of these patients have been given only the usual nonspecific supportive measures, without vasopressor or stimulant drugs, and others have received infusions of blood or plasma. The records of both groups have been reviewed in an attempt to evaluate therapy with transfusion and to form a clearer picture of the natural history of shock due to coronary occlusion.

METHODS AND MATERIALS

The records of all patients given the diagnosis of myocardial infarction since 1943 were studied. Only those with unequivocal clinical and electrocardiographic evidence of recent infarction, or those with autopsy proof of infarction, were selected for this report.

For the purposes of this study, a patient was considered to be in shock whenever the systolic blood pressure remained below 90 for at least an hour, during which the classic signs of peripheral vascular collapse (weakness or stupor, cyanosis and cold, moist skin) were present. The large group with the appearance of shock but with systolic blood pressures above 90 was not studied, even when the arterial pressure was considerably below its usual level. A few patients who looked well, although their systolic blood pressures were below 90, were not considered to be in shock. This distinction seemed to be justified by the fact that such

patients uniformly did well, whereas, as shown below, the mortality was very high among patients with the signs of vascular collapse as well as hypotension.

Tests for statistical significance were those described in Snedecor's⁹ textbook.

RESULTS

From January, 1943 to January, 1949, 325 patients with unequivocal myocardial infarction were seen in the New Haven Hospital. Some of the characteristics of the entire group are presented in Table 1 and are compared with those reported in three recent reviews.^{10, 12} It can be seen that our patients resemble those in other series in their average age, sex distribution and the incidence of diabetes and previous hypertension. Thirty-eight per cent of 120 patients selected at random showed signs of congestive heart failure. It is impossible to compare this figure with that given by other authors since the criteria for this diagnosis are not uniform. In this series, patients were considered to be in heart failure whenever they had persistent basal rales, peripheral edema or venous distention and hepatomegaly. The over-all mortality in the present group, 44 per cent, was somewhat higher than that reported by others. This may reflect the stringency of our criteria for the diagnosis of myocardial infarction, which resulted in the elimination of all doubtful, and often less serious, cases from the study.

In confirmation of many previous observations, it was found that patients with diabetes† or congestive failure had a much higher mortality than the group as a whole, whereas previous hypertension did not seem to affect the prognosis. Patients over seventy years of age had a significantly higher death rate than younger patients. The mortality was significantly higher in females than in males. This was noted previously by Mintz and Katz,¹⁰ but not by Master and his associates¹¹ or by Rosenbaum and Levine.¹² Closer examination of our data revealed that the higher mortality among women

*Only one diabetic patient was in acidosis. This patient was also in shock. The disease in all other diabetic cases in this series was well controlled.

*From the Department of Internal Medicine, Yale University School of Medicine.

†Assistant in medicine, Evans Memorial, Massachusetts Memorial Hospital; formerly assistant in medicine, Yale University School of Medicine.

Poliomyelitis Papers and discussions presented at the First International Poliomyelitis Conference Compiled and edited for the International Poliomyelitis Congress 4th, cloth, 360 pp with 92 illustrations and 52 tables Philadelphia J B Lippincott Company, 1949 \$5 00

This volume constitutes the transactions of the first world conference on poliomyelitis. There were ten sessions, and the papers read covered the whole field of the subject. The volume is essential to all medical libraries. The book is well published.

Diseases of Children Volume II Edited by Donald Paterson, M D (Edin), F R C P, consulting physician, Hospital for Sick Children, Great Ormond Street, and consulting physician in charge of diseases of children, Westminster Hospital, and Alan Moncrieff, M D (Lond), F R C P, Nuffield Professor of Child Health, University of London physician, Hospital for Sick Children, Great Ormond Street, and consulting physician, Children's Department, Middlesex Hospital. Fourth edition 8^{vo}, cloth, 1033 pp, with 380 illustrations. Baltimore: Williams and Wilkins Company, 1949 \$10 00

This second volume of a well known British treatise on pediatrics is the joint work of twenty-four contributors, specialists in their particular fields. The material covered in this volume comprises diseases of the nervous system, congenital mental defect in childhood, diseases of the eyes, diseases of the muscles, bones and joints, orthopedic surgery, diseases of the genitourinary and digestive systems and the peritoneum, rheumatism, diseases of the cardiovascular system and of the blood, infectious diseases, venereal disease and diseases of the skin, and malignant lesions in childhood. There is a good index. The text was printed in Great Britain. The treatise should be in all pediatric collections in medical libraries.

Doctors of Infamy The story of the Nazi medical crimes By Alexander Mitscherlich, M D, head of the German medical commission to Military Tribunal No 1, Nuremberg and Fred Mielke. Translated by Heinz Norden. With statements by three American authorities identified with the Nuremberg medical trial. Andrew C Ivy, M D, vice-president, University of Illinois, and medical scientific consultant to the prosecution, Military Tribunal No 1, Nuremberg, Telford Taylor, brigadier general, United States Army, Chief of Counsel for War Crimes, and Leo Alexander, M D, psychiatrist, consultant to the Secretary of War and to the Chief of Counsel for War Crimes, and a note on medical ethics by Albert Deutsch (including the new hippocratic oath of the World Medical Association) 8^{vo}, cloth, 172 pp, with 16 pages of photographs. New York: Henry Schuman, 1949 \$3 00

This book is mainly a translation of *Das Diktat der Menschenverachtung*, published by the two principal authors at Heidelberg in 1947. It constitutes the story of the famous Nuremberg medical trial of 1946-1947, before Military Tribunal No 1. The two German authors attended the trial as delegates chosen by a group of German medical societies and universities. They were treated with the utmost courtesy and accorded the same privileges as the working press, with free access to all documents and testimony. They have rendered in the main part of this book a fair and impartial report on the proceedings of the trial. The defendants comprised 20 physicians of high rank in the German organization and 3 high-ranking civilian aids, 2 of whom were formerly attached to Hitler and Himmler. The text concerns the medical experimentation carried on at various concentration camps, the collection of skulls of Jews and the euthanasia program. Seven of the defendants were acquitted and freed, 7 were sentenced to death, and 9 received prison sentences of varying lengths.

The Uses of Penicillin and Streptomycin By Chester S. Keefer, M D, Wade Professor of Medicine, Boston University School of Medicine, and director of Evans Memorial and physician-in-chief of the Massachusetts Memorial Hospitals. 8^{vo}, cloth, 72 pp. Lawrence, Kansas: University of Kansas Press, 1949 \$2 00. Porter Lectures, Series 15.

In this small volume are gathered the three Porter lectures given by Dr Keefer under the auspices of the University of Kansas School of Medicine. They present a summary of the latest knowledge on two important therapeutic agents. The first lecture is entitled "Penicillin in Medical and Surgical

Practice," the second "Streptomycin in the Treatment of Infections," and the third "Antibacterial Agents from Microbes." The last lecture comprises a short history of the subject. Dr Keefer is recognized as an outstanding authority on penicillin and similar agents. Rather surprisingly, there is a good index to the small volume. The book is well published and should be in all medical libraries.

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A Tuesday evening lecture sponsored by the Boston City Hospital House Officers' Association will be presented in the Dowling Amphitheater, Boston City Hospital, on December 13 at 7 p m. Dr Harry Eagle will speak on the subject "The Factors of Time and Dosage in the Therapeutic Use of Penicillin." The discussion will be led by Drs Maxwell Finland and Chester S. Keefer.

All interested physicians are invited to attend.

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, December 20, at 12 noon. Dr Duncan E. Reid will speak on the subject "Experiences with a Recent Medical Mission to Germany."

Physicians are cordially invited to attend.

BOSTON LYING-IN HOSPITAL OBSTETRIC ROUND TABLE

The following schedule of obstetric round-table conferences for visiting physicians will be held at the Boston Lying-in Hospital at 7 p m on the dates indicated:

December 19, 1949 Early Trimester Bleeding (Clinical, Pathological and Hormonal Aspects) Drs H. Bristol Nelson, Arthur T. Hertig and George Van S. and Olive W. Smith.

February 20, 1950 Toxemia of Pregnancy (Obstetric Management and Treatment of the Complications of Oliguria and Anuria) Drs Duncan Reid and John Merrill.

April 17, 1950 Problems of Labor in the Potentially Infected Patient (Tests of Labor, Methods of Delivery and Chemotherapy) Drs Samuel B. Kirkwood, M. Fletcher Eades and Maxwell Finland.

Visiting physicians are invited to avail themselves of the Boston Lying-in Hospital cafeteria until 6 p m.

INTERNATIONAL SOCIETY OF HEMATOLOGY

The Biennial Congress of the International Society of Hematology will be held at the University of Cambridge, Cambridge, England, August 21 through 26, 1950.

The program committee is in the process of receiving titles for papers and scientific exhibits to be presented at the Congress. Material to be submitted for consideration for the program may be sent to Dr I. Davidsohn, Mt. Sinai Hospital, Chicago, Illinois, or Dr S. Mettler, University of California, San Francisco, California. Those desiring to present scientific exhibits should make application as soon as possible.

COURSES IN RADIOISOTOPE TECHNICS

Some vacancies still remain for the winter series of three courses in radioisotope technics offered by the Special Training Division of the Oak Ridge Institute of Nuclear Studies. Interested persons who can attend a course during the winter months are urged to make application for one of these courses in view of the heavy load of applications from university people for participation in the summer courses. The courses will begin on January 2, January 30 and March 6, 1950. Applications should be made as soon as possible. Eleven of the courses have already been given. Thirty-two participants can be accommodated in each of the three four-week courses. Requests for application and additional information should be addressed to Dr Ralph T. Overman, chairman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P O Box 117, Oak Ridge, Tennessee.

(Notices concluded on page xi)

hypotension (average, seven hours) Two of these died suddenly, two and three days after emerging from shock and 3 patients survived Fifteen patients (75 per cent) died without improvement after one hour to four days in shock (average, nineteen hours), two thirds of these (10 patients) died within twelve hours

When shock was first noted, 11 (55 per cent) of the 20 patients who were not given transfusions

in 4 and improved in 3 Signs of failure followed transfusion in 2 other cases At the onset of shock, 7 patients who improved had congestive failure which, coincident with transfusion, increased in 3 and improved in 2, who were also given digitalis After receipt of 300 cc of p'lasma in twenty minutes, transient pulmonary edema developed in another patient Twelve of the 19 patients unimproved by transfusion were in congestive failure at the

TABLE 1 (Continued)

INCIDENCE OF SHOCK*	MORTALITY						
	TOTAL	MEN	WOMEN	DIABETIC PATIENTS	HYPERTENSIVE PATIENTS	PATIENTS WITH CONGESTIVE FAILURE	PATIENTS WITH SHOCK
%	%	%	%	%	%	%	%
15	44	39	55	75	46	65	88
7	22	19	29	34	21	43	78
55	29	28	32	39	29	—	—
54	33	31	35	—	36	42	44

including 2 of the 3 who survived, showed signs of congestive heart failure, usually left sided Nine of the 15 patients who died without improvement had congestive failure at this time, which improved in 1 and became worse in another In another case pulmonary edema occurred after the onset of shock In still another patient, who improved, signs of congestive failure appeared and increased temporarily before the patient recovered

The course of events was not very different in the 30 patients who received transfusions An average of 700 cc of blood or plasma was usually started three or four hours after the appearance of shock and given at the rate of 250 cc per hour Eleven of the thirty patients (37 per cent) rallied within three or four hours of the beginning of the transfusion, with an increase in systolic pressure of 10 to 60 and an improvement in general condition usually lasting until death or discharge Eight of these patients died two hours to six days after emerging from shock In 2 cases the blood pressure fell again to shock levels for a few hours before death, severe congestive failure and auricular fibrillation, with a rapid ventricular rate, developed in 1, another patient suffered a rupture of the myocardium, and 4 died suddenly of unknown cause Three patients continued to improve, 2 after repeated transfusions, and were discharged well Nineteen cases were not improved by transfusions The average survival after the beginning of shock in this group was sixteen hours This was similar to the course of patients in the "control" group who did not improve spontaneously

When transfusion was started, 19 patients (63 per cent) had congestive failure, which increased

onset of shock In only one of these did the signs of failure increase Heart failure occurred only after transfusion in another patient, who died in shock and pulmonary edema

As shown in Figure 1, more blood or plasma was given to patients who improved than to those who did not improve, however, some of the largest transfusions were not followed by improvement

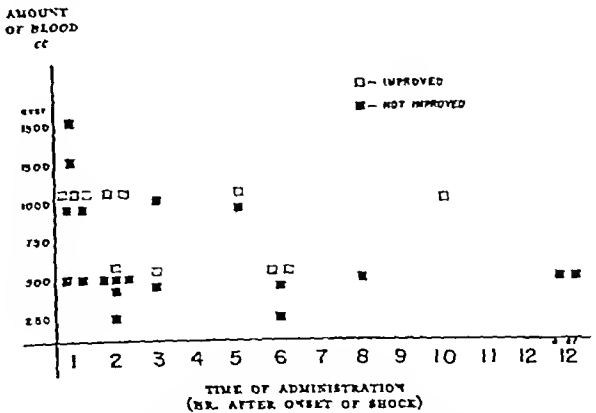


FIGURE 1 Relation of the Amount of Blood Given and the Time of Administration to Improvement in Shock

There seemed to be no relation between the presence of congestive failure and the likelihood of improvement in shock with transfusion (Table 3) Fifteen of 19 patients with congestive failure at the onset of shock had no increase in failure with transfusion Indeed, congestive failure increased almost as often in patients who were not given transfusions (15 per cent) as in those receiving transfusions (20 per cent)

was apparently due to the greater age of our female patients and their higher incidence of diabetes. There was no significant difference in the mortality of the two sexes when only nondiabetic patients or diabetic patients in the same age group were compared.

Fifty patients, or 15 per cent of the series, satisfied the arbitrary criteria for shock outlined above. This figure is not comparable with those in the other

The average age and the incidence of previous hypertension in the patients in shock who received transfusions resembled those in patients in shock who did not get blood or plasma. As judged by the frequency of congestive failure, recurrence of pain after admission, occurrence of arrhythmia or intraventricular block and the average white-cell count and average temperature, the two groups did not differ significantly in the severity of the

TABLE 1 Incidence of Some Clinical Features in Patients with Coronary Occlusion and Their Effect on Mortality

AUTHOR	NO OF CASES	PROPORTION OF MEN TO WOMEN	AVERAGE AGE	INCIDENCE OF DIABETES	INCIDENCE OF HYPERTENSION	INCIDENCE OF CONGESTIVE FAILURE
		%	yr	%	%	%
Epstein and Relman	325	68 32	61	15	48	38†
Mintz and Katz ¹²	572	68 32	60	16	36	23
Master et al ¹¹	500	77 23	55	11	62	51
Rosenbaum and Levine ¹⁴	208	69 31	59	—	57	70

*"Shock" not defined by other authors.
†120 cases at random.

series because no precise definition of shock is given by their authors. The mortality in this group was 88 per cent—more than twice that of the other patients not in shock. Thirty of the patients in shock were given transfusions of blood or plasma, and the remaining 20 were not. Table 2 compares certain features of the patients in shock with those not in shock and also compares the 30 pa-

myocardial insult. Their selection differed strikingly in that all diabetic patients in shock were given transfusions, comprising nearly half the transfusions. This factor must be considered when the results in the patients receiving transfusions are compared with their "controls" because the presence of diabetes (even though regulated) carried an extremely high mortality regardless of the presence of shock.

TABLE 2 Data on Patients with and without Shock

TYPE OF CASE	NO OF CASES	AVERAGE AGE	RATIO OF MEN TO WOMEN	MORTALITY	INCIDENCE OF HYPERTENSION	INCIDENCE OF DIABETES	INCIDENCE OF CONGESTIVE FAILURE	HIGHEST WHITE CELL COUNT	HIGHEST TEMPERATURE	INCIDENCE OF RECURRENT PAIN	INCIDENCE OF ARRHYTHMIA
		yr	%	%	%	%	%	$\times 10^3$	$^{\circ}F$	%	%
Patients in shock											
Transfusion* given	30	62	63 37	90	43	47	70	18 05	100 0	40	67
No transfusion given	20	61	75 25	85	50	0	65	17 58	100 5	35	65
Total	50										
Averages		62	68 32	88	46	28	68	17 80	100 2	—	—
Patients without shock	275	61†	71 29†	35	49†	14	38‡	14 40	100 9	—	—

*There were no significant differences between patients who received transfusions and those who did not, except for the incidence of diabetes.
†No statistically significant difference.
‡120 cases at random.

tients receiving transfusions with the 20 treated by more conventional methods.

Patients in shock had essentially the same age and sex distributions and the same incidence of previous hypertension as those not in shock. However, they had twice the incidence of diabetes and of congestive failure. The patients in shock had a significantly higher average white-cell count and lower temperature than the rest of the series.*

*The highest white-cell count and the highest temperature occurring during the first three days of hospitalization were recorded. Temperatures were usually taken by rectum but sometimes (and perhaps more often in the sickest patients) by mouth.

From the 20 patients who went into shock and were not given transfusions it was possible to form a picture of the natural history of the shock of myocardial infarction under the usual treatment. Table 3 summarizes the clinical course in the two groups.

At any time up to 12 days after the onset of chest pain (but within twenty-four hours in three quarters of the cases), the patients who were not given transfusions exhibited the signs and symptoms of peripheral vascular collapse. Five patients (25 per cent) improved after two hours to three days of

hypotension (average, seven hours) Two of these died suddenly, two and three days after emerging from shock, and 3 patients survived Fifteen patients (75 per cent) died without improvement after one hour to four days in shock (average, nineteen hours), two thirds of these (10 patients) died within twelve hours

When shock was first noted, 11 (55 per cent) of the 20 patients who were not given transfusions

in 4 and improved in 3 Signs of failure followed transfusion in 2 other cases At the onset of shock, 7 patients who improved had congestive failure, which, coincident with transfusion, increased in 3, and improved in 2, who were also given digitalis After receipt of 300 cc of plasma in twenty minutes, transient pulmonary edema developed in another patient Twelve of the 19 patients unimproved by transfusion were in congestive failure at the

TABLE 1 (Continued)

INCIDENCE OF SHOCK*	MORTALITY			MORTALITY			
	TOTAL	MEN	WOMEN	DIABETIC PATIENTS	HYPERTENSIVE PATIENTS	PATIENTS WITH CONGESTIVE FAILURE	PATIENTS WITH SHOCK
%	%	%	%	%	%	%	%
15	44	39	55	73	46	65	88
7	22	19	29	33	25	43	78
53	29	28	32	39	29	—	—
54	33	31	35	—	36	42	44

including 2 of the 3 who survived, showed signs of congestive heart failure, usually left sided Nine of the 15 patients who died without improvement had congestive failure at this time, which improved in 1 and became worse in another In another case pulmonary edema occurred after the onset of shock In still another patient, who improved, signs of congestive failure appeared and increased temporarily before the patient recovered

The course of events was not very different in the 30 patients who received transfusions An average of 700 cc of blood or plasma was usually started three or four hours after the appearance of shock and given at the rate of 250 cc per hour Eleven of the thirty patients (37 per cent) rallied within three or four hours of the beginning of the transfusion, with an increase in systolic pressure of 10 to 60 and an improvement in general condition usually lasting until death or discharge Eight of these patients died two hours to six days after emerging from shock In 2 cases the blood pressure fell again to shock levels for a few hours before death, severe congestive failure and auricular fibrillation, with a rapid ventricular rate, developed in 1, another patient suffered a rupture of the myocardium, and 4 died suddenly of unknown cause Three patients continued to improve, 2 after repeated transfusions, and were discharged well Nineteen cases were not improved by transfusions The average survival after the beginning of shock in this group was sixteen hours This was similar to the course of patients in the "control" group who did not improve spontaneously

When transfusion was started, 19 patients (63 per cent) had congestive failure, which increased

onset of shock In only one of these did the signs of failure increase Heart failure occurred only after transfusion in another patient, who died in shock and pulmonary edema

As shown in Figure 1, more blood or plasma was given to patients who improved than to those who did not improve, however, some of the largest transfusions were not followed by improvement

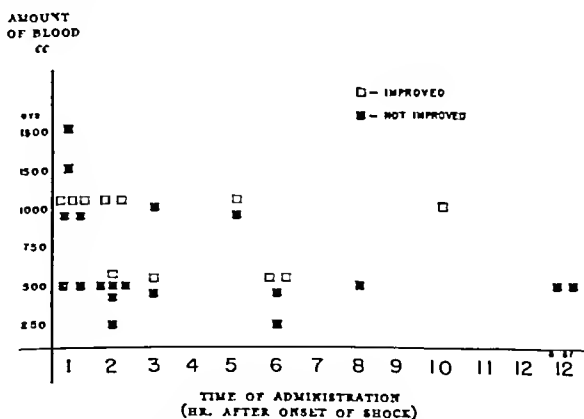


FIGURE 1 Relation of the Amount of Blood Given and the Time of Administration to Improvement in Shock

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In summary, from a purely statistical comparison of two small groups, no benefit from transfusion could be demonstrated. These figures are weighted by the fact that nearly half the patients receiving transfusions had diabetes, and presumably a worse initial prognosis than those not transfused, none of whom had diabetes. However, in this condition, in which every case is unique and the natural mor-

The situation had not changed 3 hours later, when an infusion was started. A liter of whole blood, a liter of 10 per cent glucose solution and 300 cc of physiologic saline solution were administered over the next 12 hours. Four hours after the transfusion had begun, when 500 cc of blood had been given, the blood pressure rose to 138/110. After the administration of another 500 cc of blood it was 150/110, and the patient looked and felt better. There was no increase in dyspnea or pulmonary rales. Four hours after the infusion had been stopped, the blood pressure began to drop again, and 3 hours later it was 100/86. Eight hours after transfusion

TABLE 3 Clinical Course of Patients in Shock

GROUP	NO OF CASES	DEATHS	IMPROVEMENT IN SHOCK			NO IMPROVEMENT IN SHOCK			FAILURE INCREASED
			PATIENTS WITH HEART FAILURE*	PATIENTS WITHOUT HEART FAILURE	TOTALS	PATIENTS WITH HEART FAILURE	PATIENTS WITHOUT HEART FAILURE	TOTALS	
Patients receiving transfusions	30	27 (90%)	8	3	11 (37%)	13	6	19 (63%)	6 (20%)
Patients not receiving transfusions	20	17 (85%)	3	2	5 (25%)	10	5	15 (75%)	3 (15%)

*Congestive heart failure at any time after onset of shock

tality very high, statistical summaries may be less informative than a careful study of individual cases. Despite the statistical similarity between the transfused and "control" groups, transfusion seemed to be responsible for the clinical improvement in some patients. The following case reports are representative of 11 cases in which transfusion was accompanied by improvement in the shock syndrome.

A M (B60512), a 57-year-old man with hypertension, mild heart failure and one previous myocardial infarction, was admitted to the hospital after several hours of agonizing chest pain. The electrocardiogram was typical of recent anterior myocardial infarction. The blood pressure was 100/70. The first day of hospitalization was complicated by a nodal tachycardia, which subsided after large doses of quinidine. Thirty-two hours after admission, the arterial pressure dropped to 80/60, the patient became semistuporous, and his skin was cyanotic and clammy. He had not voided since admission. After 4 hours in this state, 1000 cc of plasma was given intravenously over a period of 2 hours. The blood pressure rose to 90/70. Even though the venous pressure rose from the equivalent of 210 mm to 340 mm of water, there was no increase in dyspnea or pulmonary rales, and the patient looked improved. Six hundred cubic centimeters of urine was obtained shortly after the infusion was completed. The blood pressure remained at 90/70 until 16 hours later, when it again fell to 80/60 and another 500 cc of plasma was infused. The venous pressure rose from the equivalent of 240 mm to 300 mm of water, but the patient seemed more alert and was able to void adequate amounts of urine. The blood pressure rose to 105/70 and was maintained at that level until discharge, 4 weeks later, when the signs of congestive failure had cleared.

A I (A57425), a 50-year-old diabetic man with hypertension and polycythemia, who had suffered a previous myocardial infarction, was admitted because of increasing dyspnea of 1 week's and vomiting of 1 day's duration. The arterial pressure was 150/120. He was digitalized because rales were present at the lung bases. Eighteen hours after admission severe, squeezing pain in the anterior portion of the chest developed, his blood pressure dropped to 80/40, and his extremities became cold and clammy. The concentration of glucose in the blood was not determined at this time, but hypoglycemia was considered unlikely because he had been given only 15 units of crystalline insulin 16 hours previously, and this had been followed by an infusion of glucose solution

had been stopped, the patient died. Autopsy confirmed the presence of a recent myocardial infarction.

DISCUSSION

Profound shock eventually results in widespread, irreversible disorganization of bodily function.¹⁴ In the presence of recent myocardial infarction, shock is particularly pernicious because existing cardiac damage may be aggravated by further reduction of coronary blood flow.^{14, 16} Most authorities agree, therefore, that this situation calls for prompt measures aimed at raising arterial pressure.

When shock follows experimental coronary occlusion in dogs, cardiac output is usually lowered but often not in proportion to the changes in arterial pressure.^{17, 18} By contrast with traumatic shock, the blood volume and central venous pressure are not reduced.^{17, 18} The meager data available on the hemodynamic changes occurring in man also indicate that, although the cardiac output may be reduced, neither the blood volume nor the central venous pressure is low.¹⁹ However, in some cases, there is evidence of peripheral venous collapse.^{20, 21} Two cases of shock and congestive failure following myocardial infarction have been reported in which the cardiac output was within normal limits in the presence of an elevated filling pressure.^{22, 23} Obviously, much more data of this sort is needed to clarify the mechanism of coronary shock in man.

Some authors^{6, 24} argue that the most rational therapy is the use of cardiac stimulants and vasoconstrictor drugs, but few cases of their successful employment have been reported.^{2, 24} One might expect blood transfusions to be of value if this type of shock were associated with pooling of blood in the splanchnic vessels and diversion of the circulation from more vital areas. There is evidence that this does occur in experimental hemorrhagic shock.

in dogs^{25, 26} and in shock due to mechanical limitation of blood flow²⁷

Transfusion might improve the circulation if further elevation of an already high venous filling pressure could increase the output of an infarcted heart. It has been shown that this occurs in a dog's heart failing during post-hemorrhagic shock after replacement of blood volume, although such a heart is less capable of responding to a given increment in filling pressure than it was before hemorrhage.^{28, 29} The blood pressures of 8 patients in this study rose during transfusion despite the presence of congestive failure. This suggests that some of these patients responded to augmented cardiac filling with an increase in cardiac output or peripheral resistance.

Many authors warn against transfusion of patients in shock when heart failure is present.³⁰⁻³² In only 2 of 21 such cases did pulmonary edema follow transfusion, and in one of these the symptoms subsided within half an hour, and the blood pressure rose. Signs of heart failure increased among the control patients almost as often as they did in those given transfusions. These data therefore suggest that transfusions can be given with relative safety.

It should be emphasized, however, that most of our patients received smaller quantities of blood at slower rates than are usually necessary to treat hemorrhagic and traumatic shock. For this reason the present study is inconclusive. Although more vigorous therapy might have improved the results, it is also possible that pulmonary edema would have been a more frequent complication. A more definitive investigation should include detailed hemodynamic studies on patients treated with larger and more rapid infusions than those employed in the present report. That such an effort is feasible is suggested by the infrequent development of pulmonary edema after transfusion in this series.

SUMMARY

Clinical observations on the effect of transfusions in 30 patients with shock following coronary occlusion are compared with the natural history of the disease in 20 patients not given transfusions.

Although transfusion seemed to be of benefit in a few cases there was no significant difference between the two groups in mortality and recovery from shock.

Transfusion did not seem to increase the incidence of pulmonary edema or the severity of congestive failure.

Shortly after this paper was submitted for publication, Sampson and Singer³³ reported their experience with small transfusions in the treatment of 11 cases of coronary shock. In spite of transient improvement in 8 cases only 1 patient survived his illness. Maximum improvement seemed to be dependent on early and fairly rapid transfusion. One patient with an initially high peripheral venous pressure died in pulmonary edema, but all others with congestive heart failure tolerated the transfusions well.

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B.C.G. TUBERCULIN AS A TESTING MATERIAL*

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BOSTON

WITHOUT going into a lengthy discussion on the significance of a positive skin reaction to tuberculin and its limitations, it is fair to state that few laboratory tests are as satisfactory and as widely used by the medical profession. Any additional contribution to the safety and efficiency of the test should be of value.

It is well known that the allergic response to tuberculoprotein, as indicated by the intensity of the reaction to tuberculin, varies in different persons. Thus, a given amount of tuberculin may elicit a mildly positive reaction in one subject and yet, in a more sensitive person, may cause a severe local reaction with vesiculation and necrosis, as well as constitutional symptoms such as malaise, chills and fever. The possibility, furthermore, of focal reactions with reactivation of a latent focus of tuberculosis, though very rare, must be kept in mind.

To avoid these severe reactions, it has been customary to start with a small initial dose, and, so that positive reactions in less sensitive persons will not be overlooked, this initial dose is followed by one or more tests with larger amounts of old tuberculin (O.T.) or purified protein derivative (P.P.D.). O.T., as is well known, is a steam-concentrated, glycerin-broth culture of human tubercle bacilli passed through a porcelain filter. P.P.D. is the heated protein of tubercle bacilli that has been precipitated from human tubercle bacilli cultured on protein-free mediums. The initial dose of O.T. is usually 0.1 cc. of a 1:1000 dilution (0.1 mg.). The second test is with 0.1 cc. of a 1:100 dilution (1.0 mg.). The dosages of P.P.D. as now marketed are as follows: first testing dose, 0.00002 mg., and second dose, 0.005 mg.

There is, however, an upper limit on the amount of tuberculin one can use. Smith et al.¹ carried out studies demonstrating that false-positive reactions, or "pseudoreactions," are obtained in as many as 15 per cent of cases when large doses (10 mg.) of O.T. are used. Some observers believe that any dose of O.T. over 1.0 mg. is unreliable because of the high incidence of false reactions. Furcolow et al.,² working with P.P.D., reported pseudoreactions in 50 per cent of cases when the usual second test dose (0.005 mg.) was used and the remarkably high figure of 96 per cent false reactions with the use of 1.0 mg. Vollmer³ states that, even

with the Patch test, pseudoreactions are more common when the concentration is increased.

It is obvious that the ideal tuberculin would be one that is free from severe positive reactions as well as pseudoreactions. In an effort to inhibit severe positive reactions, we tried antihistamine drugs⁴ and found them to be unsatisfactory.

It then occurred to us that a tuberculin prepared from B.C.G. vaccine might be an improvement over previous tuberculins. The bacilli in B.C.G. vaccine are sufficiently attenuated to be nonpathogenic and yet have not lost their ability to convert nonreactors to positive reactors. It was therefore decided to study the efficiency of B.C.G. tuberculin as compared with commercial tuberculin.

MATERIALS AND METHODS

This study was carried out with children aged four to twelve years at the Prendergast Preventorium in Mattapan, Massachusetts. Dr. Konrad Birkhaug, of the Division of Laboratories and Research of the New York State Department of Health, kindly prepared and supplied us with B.C.G. and O.T. The latter was prepared on a 5 per cent glycerolated broth, whereas the B.C.G. tuberculin was produced from an eight-week-old culture of B.C.G. grown on Sauton's (protein-free) synthetic medium. The concentration of these two tuberculins, according to Dr. Birkhaug, was comparable.

The children were tested intracutaneously with similar amounts of both O.T. and B.C.G. tuberculin. The same location (midvolar surface of the left and right forearms) was used for all injections. Alternate arms were used for B.C.G. and O.T. on every other subject so as to avoid any possible difference in reactivity of the right and left arms. The reactions were read at intervals of twenty-four, forty-eight and seventy-two hours, and those showing an induration of 5 mm. or more in diameter at the end of forty-eight hours, in addition to varying amounts of erythema, were considered positive reactions. (This is a criterion for reading a positive test as recommended by the Massachusetts Department of Public Health).⁵ The length and width of the indurations were measured with a millimeter rule. The product of these two measurements was considered as the area of the reaction and sufficiently accurate since the error would be approximately the same in all readings.

RESULTS

Of 91 children tested simultaneously with both 1:10,000 O.T. and 1:10,000 B.C.G. tuberculin, 43

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were positive with both testing materials, and 48 were negative with both agents. The positive reactions were much more severe with OT in all but 8 cases of the 43 (Table 1). These 8 cases showed an equally mild reaction on both arms. Vesiculation occurred in 6 cases with the use of OT, whereas the opposite arm with BCG showed a definite positive reaction but without severity or vesiculation.

The 48 negative reactors were retested with a 1:100 dilution of both tuberculin on opposite arms

TABLE 1 Comparative Intensity of Positive Tuberculin Reactions

SUBJECT	AREA OF REACTION	
	WITH O.T. 1:10,000	WITH B.C.G. 1:10,000
	sq. cm.	sq. cm.
J. L.	0.4	0.3
D. W.	1.4	0.3
D. M.	4.0*	1.0
B. M.	4.1	1.0
P. D.	4.0	1.2
R. D.	3.0	0.9
J. J.	4.4	0.3
M. M.	3.2	0.3
B. M.	1.1	0.4
F. C.	3.3	0.6
R. M.	3.0*	0.4
J. D.	1.2	0.9
D. E.	3.0	2.1
F. D.	1.9	1.0
J. D.	1.0	1.0
W. S.	3.0	0.3
S. F.	2.7	0.4
S. F.	0.3	0.3
W. C.	2.0	0.3
A. M.	4.4	0.7
D. M.	3.0	0.6
V. W.	3.4	0.4
L. F.	2.3	0.8
L. N.	1.0	0.7
R. P.	4.1	3.6
A. W.	6.0	0.3
A. T.	4.3*	0.5
M. M.	3.6	0.3
P. H.	5.0*	0.6
J. G.	6.0	0.4
D. W.	3.3	0.5
C. M.	1.0	0.6
C. F.	4.0	1.7
P. G.	3.0	0.5
R. D.	0.5	0.5
D. K.	1.4	1.0
E. B.	5.0*	3.8
M. T.	5.1	3.8
S. M.	7.0	2.1
D. E.	3.0	0.4
M. M.	1.7	0.6
	2.5	0.6

*Vesiculation.

Here again BCG proved to be as accurate as OT. Three subjects were found to be mildly positive to both. Pseudoreactions were much more common with OT and took forty-eight hours or more to fade, whereas with BCG these false-positive reactions were much less frequent and less severe and faded much more quickly.

In the final phase of the study 10 known positive reactors were tested with 1:100 dilution of OT, after which they were retested with a 1:100 dilution of BCG tuberculin. The difference in reactions was marked (Table 2). In 6 of the 10 OT-tested children vesicles, mild necrosis with markedly sore

arms and temperatures ranging from 101 to 104°F developed. The tests with BCG were all definitely positive, none were borderline, but were without

TABLE 2 Comparative Intensity of Positive Tuberculin Reactions

SUBJECT	AREA OF REACTION*	
	WITH O.T. 1:100	WITH B.C.G. 1:100
	sq. cm.	sq. cm.
J. J.	9.0†	6.2
M. M.	9.0†	9.0
V. L.	2.2	2.2
D. K.	9.0	4.0
P. D.	16.0†	4.0
D. W.	4.0	4.0
D. S.	9.0†	2.2
P. G.	4.0	4.0
R. D.	9.0†	4.0
L. N.	9.0†	4.0

*Length and width of induration

†Vesiculation and temperature of 101 to 104°F

vesiculation and were unaccompanied by fever or other constitutional symptoms.

DISCUSSION

BCG tuberculin proved to be as accurate as OT since, despite the greater severity of the reactions with the latter, the tests all ran parallel in regard to positiveness or negativeness. In the dilution of 1:100 the reactions to BCG tuberculin were so definitely positive that there was no question of interpretation and no need for further testing with still larger doses. It is possible that a smaller dose of BCG tuberculin would be even more satisfactory as an initial and single testing strength material, thereby reducing still further the incidence of severe positive reactions and pseudoreactions. An optimum dose for routine intracutaneous testing, depending of course, on further observation and standardization, probably lies in a dilution between 1:1000 (0.1 mg.) and 1:200 (0.5 mg.). From our observations thus far, a dilution of 1:500 (0.2 mg.) appears to be the preferred dose.

The difference between the two tuberculin cannot properly be explained on the basis that BCG tuberculin is derived from bovine and OT from human tubercle bacilli, because it has been demonstrated by numerous observers that bovine and human tuberculin share a common antigen.

Nor can one ascribe all the differences in the severity of the reactions to the dissimilarity in the mediums used in the preparation of the two tuberculin. It is true that Magnusson and Lithander⁵ found that the glycerolated broth, which is the medium used for the preparation of OT, will give larger and more frequent reactions than Sauton's (protein-free) synthetic medium, which is used for the preparation of BCG tuberculin, but it is doubtful if this has any perceptible effect upon the real tuberculin reactions read in forty-eight to seventy-two hours.

It is very likely that the difference between the two tuberculins is qualitative as suggested by the work of Magnusson and Lithander.⁵ They found that in BCG-vaccinated children BCG tuberculin will provoke reactions considerably earlier and more frequently than OT. A better understanding of this qualitative difference may give more insight into the relation between allergy and immunity in tuberculosis.

SUMMARY AND CONCLUSIONS

From preliminary observations, it is fair to conclude that BCG tuberculin is a reliable and safe testing material. With similar dosages, given intracutaneously, BCG tuberculin produced much less severe positive reactions without undesirable local and constitutional manifestations and fewer

pseudoreactions than were seen with the use of OT.

Pending further standardization of the proper dosage, BCG tuberculin should prove to be suitable as a single-strength tuberculin for routine testing. This, it is hoped, would obviate, except in rare cases, the necessity for the present method of repeated testing.

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OBSERVATIONS ON THE SYMPTOMATIC TREATMENT OF CHRONIC VASCULAR HEADACHE WITH CAFERGONE (ERGOTAMINE TARTRATE AND CAFFEINE)*

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THE migrainous patient is grateful for any medication that will afford him symptomatic relief. Until recently, about the only medication capable of offering him any appreciable degree of comfort was ergotamine tartrate. Within the past year, a new preparation, Cafergone,§ has become available. This product contains a combination of ergotamine tartrate and caffeine.

Ergotamine is a natural alkaloid derived from ergot, a fungus found growing upon rye and other grains. Its pharmacologic actions¹ in man can be briefly outlined as follows: increase in contractions of the uterus by direct stimulation of the uterine musculature, constriction of smaller blood vessels, which is probably due to a direct peripheral action on the vascular muscle and consequent increase in the blood pressure, bradycardia, which may be a reflex response to vasoconstriction or a result of the ability of ergotamine to inactivate cholinesterase, a variable and minor effect on the central nervous system, a damaging effect on capillary endothelium with resultant vascular stasis, thrombosis and tissue gangrene—the mechanism of this action is not completely understood but may be secondary to extreme vasoconstriction and slowing of the blood stream with subsequent endothelial injury (Yater and Cahill² found that gangrene

was due to occlusion of the medium-sized and small arteries and arterioles by severe constriction and thrombus formation, intimal proliferation also possibly playing a role), and an adrenergic blocking effect³ on the sympathetic nervous system through paralysis of the excitatory responses (and possibly the inhibitory responses also) to epinephrine and adrenergic nerve impulses. Ergotamine does not prevent the liberation of the chemical mediators (adrenin or sympathin) but prevents the effector cells from responding to this substance.¹ Its action in providing symptomatic relief in migraine is so specific that this therapeutic response is often used as a diagnostic sign of migraine. It exerts no sedative or analgesic action so that it is only rarely that other types of headaches will be relieved by this drug. The most probable explanation of its therapeutic effect is based upon the concept of migraine as expressed by Wolff,⁴ in that the pain associated with migraine is due to dilatation and distention of relaxed cranial arteries, primarily branches of the external carotid artery. The therapeutic effect of ergotamine tartrate depends upon its specificity of action in its ability to constrict these relaxed and distended vessels.

Caffeine (1,3,7 trimethyl xanthine) is a derivative of coffee seeds and tea leaves. Its pharmacologic actions¹ can be briefly outlined as follows: stimulation of the central nervous system, especially the cortex (psychic and sensory functions and motor activity) and the medulla (respiratory, vasomotor and vagal centers), stimulation of the myocardium

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directly resulting in tachycardia, increased cardiac output and a slight rise in blood pressure or a reflex bradycardia by inhibition of the medullary vagal nuclei, dilatation of peripheral blood vessels by a direct effect on the vascular musculature or constriction of these vessels by central stimulation of the medullary vasomotor centers^{1,5}, relaxation of coronary blood vessels, relaxation of smooth-muscle spasm, especially that of the biliary tract and bronchi, stimulation of skeletal muscles, slight increase in the basal metabolic rate, and a diuretic effect. The action is not completely understood, but the drug is believed to accomplish this by decreasing tubular reabsorption of fluid. Caffeine has been reported to be occasionally effective in headaches and migraine. This may be related to changes that the drug produces in the cerebral circulation.¹ Wolff⁴ reports that a mixture of caffeine and sodium benzoate administered intravenously acts as a vasodilator, whereas when given orally with a slower rate of absorption it may act as a vasoconstrictor. Thus, it may afford relief in migraine through its vasoconstricting action, for Wolff⁴ has found that other agents, which decrease the amplitude of pulsations of the cranial arteries, may lessen and abolish the headache of migraine when they reduce the amplitude to a degree comparable with the reduction produced by ergotamine tartrate. Goltman,⁶ by directly observing the bulging edematous brain during a migraine attack in a patient with an operative skull defect, and Redisch and Pelzer,⁷ who examined the capillaries in the skin at the cuticle base and in the mucosa of the lower lips in patients during migraine attacks induced by forced water intake, present evidence that migraine may be associated with changes in water metabolism and retention of fluids. The diuretic action of caffeine could therefore furnish one explanation for its therapeutic effect in cases of migraine. Dreisbach and Pfeiffer⁸ have demonstrated a "caffeine withdrawal headache" which may result from distention of the cranial arteries. The basic mechanism of this painful vasodilatation is obscure but may in some way be related to the sudden withdrawal of a central vasoconstricting agent, or accompanied by a relative increase in the effective blood volume.

Patients suffering from migraine have found that black coffee will enhance the effect of ergotamine tartrate or afford a certain degree of relief by itself. This, together with the known pharmacologic vasoconstricting and diuretic action of caffeine, resulted in the combination of ergotamine tartrate and caffeine for use in the symptomatic treatment of migraine. Friedman and Brenner,⁹ in studying 94 patients with migraine treated with various agents, report that combinations of ergotamine tartrate with caffeine proved to be more effective in relieving the migraine attack than ergotamine tartrate alone. Horton, Ryan and Reynolds,¹⁰ re-

porting 55 cases of headache, state that 56 per cent of patients obtained excellent results and 24 per cent obtained some relief with E C 110 (Cafergone) and that practically all the patients studied believed that E C 110 was more effective than ergotamine alone.

The following report deals with our results obtained with the use of this preparation.

CLINICAL MATERIAL

Fifty patients with chronic vascular headache were given a therapeutic trial with Cafergone. This was administered in oral tablets (E C 110) and in the form of a rectal suppository (E C 112). The oral preparation contained 100 mg of caffeine and 1 mg of ergotamine tartrate. The dosage was three tablets immediately during the aura or at the first warning of an impending headache and then one every half hour as needed for three subsequent doses, the total dosage not exceeding six tablets. In this group of patients there was a young boy, eleven years of age, to whom the drug was effectively administered in half this dosage. For patients who had extreme nausea and vomiting as a side effect of ergotamine or as part of the migrainous attack and who could not retain an oral preparation, the medication was supplied in the form of a rectal suppository. Each suppository contained 100 mg of caffeine and 2 mg of ergotamine tartrate. One suppository was used immediately upon the first warning of the onset of the headache, and then one every half hour as needed for two subsequent doses, the total dosage not exceeding three suppositories. A course of therapy was not repeated more often than once every ten days. Each of the patients was given at least two trials of therapy before definite evaluation was established.

Results were evaluated and tabulated as follows: none — no relief obtained, doubtful — doubtful

TABLE 1 *Results of Treatment of 50 Patients with Chronic Vascular Headache*

TYPE OF HEADACHE	NO OF PATIENTS	RELIEF OBTAINED WITH CAFERGONE	NO RELIEF OBTAINED WITH CAFERGONE
		NO OF PATIENTS	NO OF PATIENTS
Histaminic	2	2	0
Allergic	4	3	1
Migraine	44	37	7
Totals	50	42	8

relief after a complete course of medication, mild — mild relief after a course of medication, moderate — moderate relief after a partial course of medication or definite relief after a complete course of medication, and marked — marked and definite symptomatic relief after two or three tablets or one suppository, each time the medication was employed.

Table 1 summarizes the findings.

Histaminic Cephalgia

Cafergone was administered to 2 patients with typical histaminic cephalgia as described by Horton¹¹ The symptomatology of this syndrome was characterized by unilateral headaches, of short duration, with sudden onset and cessation, often occurring at night, and associated with rhinorrhea, lacrimation, flushing and sweating of the forehead on the same side. One patient achieved an effective response varying between mild and marked, and in the second case marked relief of symptoms was noted.

Allergic Headache

Cafergone was given to 4 patients with typical allergic headache as described by Eyermann¹² The criterion for diagnosis of this condition was a non-migrainous type of vascular headache, with diffuse head pain, brought about as a result of the ingestion of a food or drug in a sensitive patient often suffering with an associated allergic disorder. In this group, 1 patient obtained no relief with this preparation, whereas the other 3 noted moderate relief with both the oral and suppository forms. One patient in this group also had Ménière's syndrome of allergic etiology associated with the cephalgia. It is interesting to note that Cafergone resulted in complete relief of the headache but did not affect the symptomatology of the Ménière syndrome.

Migraine

In this series of patients there were 44 cases of migraine. Thirty-six patients had the typical vasodilating type of migraine with the characteristic

TABLE 2 Degree of Relief Obtained with Cafergone in 44 Patients with Migraine

RELIEF	NO OF PATIENTS
None	7
Doubtful	2
Mild	5
Moderate	17
Marked	13

paroxysmal, periodic, recurrent, unilateral headaches, throbbing in nature, preceded by an aura and scotomas and associated with nausea, vomiting and photophobia. In 8 cases one or more of these features of the classic pattern were lacking, so that the established diagnosis was atypical migraine. Thirty-four patients were females, and 20 males were included in this series. Their ages ranged from eleven to fifty-nine years. The condition had been present from two and a half years to fifty years. The etiology of the migraine in these patients varied, with 25 cases due to allergy in this

group. This in no way reflects the true incidence of allergy as the cause of the migraine, for allergy usually produces this syndrome in a much smaller percentage of cases. It should be pointed out that the reason that the migraine could be attributed to allergy in such a large percentage of our patients

TABLE 3 Cafergone Compared with Ergotamine Taken Orally in 32 Patients

ERGOTAMINE TARTRATE SUPERIOR	CAFERGONE SUPERIOR	NO DIFFERENCE NOTED	NO RELIEF OBTAINED WITH EITHER DRUG
NO OF CASES	NO OF CASES	NO OF CASES	NO OF CASES
2	22	4	4

was that they were attending an allergy clinic, by reason of referral from another department that had suspected an allergic etiology or because they were allergic persons receiving treatment in this clinic for associated allergic diseases.

The therapeutic results achieved with Cafergone in this series of patients are summarized in Table 2, 3, 4 and 5.

In the total series of 44 patients with migraine, 37 noted relief of symptoms with the use of Cafergone.

TABLE 4 Comparison of the Efficacy of Cafergone Administered Orally (E. C. 110) and by Rectal Suppository (E. C. 112) in 25 Patients

ORAL TABLETS (E. C. 110) SUPERIOR	RECTAL SUPPOSITORIES (E. C. 112) SUPERIOR	NO DIFFERENCE NOTED
NO OF CASES	NO OF CASES	NO OF CASES
11	8	6

gone, and 7 reported no relief. In the cases in which no relief was obtained, 3 patients had symptoms of classic migraine, and 4 had atypical migraine. Of the 8 patients in the entire group suffering with atypical migraine, 4 noted relief of symptoms, and

TABLE 5 Analysis of 33 Patients with Migraine Previously Treated with Ergotamine Tartrate

PREVIOUS RELIEF WITH ERGOTAMINE TARTRATE	PATIENTS WHO OBTAINED RELIEF WITH CAFERGONE AFTER NO RELIEF WITH ERGOTAMINE	PATIENTS WHO DID NOT OBTAIN RELIEF WITH CAFERGONE AFTER NO RELIEF WITH ERGOTAMINE
NO OF CASES	NO OF CASES	NO OF CASES
22	8	3

4 experienced no relief after a course of Cafergone. It is noteworthy that one patient in whom Cafergone was effective reported that the only thing that had given her relief prior to this was black coffee. Another stated that antihistaminics were

more effective than either ergotamine or Cafergone. It is also interesting to point out that in 1 case in which a marked therapeutic effect was achieved with Cafergone, the patient reported an accompanying diuresis each time this preparation was employed.

Eight patients exhibited side reactions with the oral medication. Five who manifested gastrointestinal reactions noted absence of these side effects when switched to the rectal-suppository form, and only 3 of these patients also had side reactions to the suppository as well. Among the side effects listed were nausea, vomiting, irritability, feverishness, paresthesias and weakness. These side reactions, especially nausea and vomiting, were effectively controlled with 0.4 mg (1/150 gr) of atropine sulfate, administered by hypodermic injection or with tincture of belladonna (10 to 15 drops) when symptoms were less severe.

DISCUSSION

From the data presented above, it appears that preparations containing ergotamine tartrate combined with caffeine are effective in the symptomatic treatment of migraine. The addition of caffeine to the ergotamine tartrate in all probability exerts a synergistic action through either its vasoconstrictor or its diuretic effect. It appears that some patients who find no relief with ergotamine tartrate taken orally may achieve some degree of symptomatic relief with Cafergone. Many patients who find the oral preparation of ergotamine effective in the treatment of their migraine now find that Cafergone affords them a still greater degree of relief of symptoms. Some patients who obtain symptomatic relief only with ergotamine tartrate administered subcutaneously now find that Cafergone will achieve a similar therapeutic response, and it is therefore preferred by many of these patients because of the elimination of the necessity of a hypodermic injection. However, there are still many patients suffering with migraine who find that ergotamine tartrate by hypodermic injection is the only medication that will afford any appreciable degree of symptomatic relief. Like ergotamine, Cafergone is most effective when given during the period of aura or at the first warning of an impending headache rather than after the symptoms of migraine are well established. Its chief value lies in aborting the syndrome in its early stages. It is of no value in vasoconstrictive ("white") migraine, in which the indicated therapeutic agent to be employed is a vasodilating drug. Its side actions are essentially similar to those of ergotamine. Nausea and vomiting are effectively controlled with atropine sulfate, administered subcutaneously, and the muscle pains and weakness of the extremities are relieved by the intravenous administration of 10 cc of 10 per cent calcium gluconate. Often, when the patient can tolerate nothing by mouth

because of extreme nausea and vomiting, simply switching to the rectal suppository form of this preparation will result in symptomatic relief.

The contraindications to the use of Cafergone are essentially similar to those of ergotamine. Prolonged usage and overdosage can lead to the symptoms of ergot poisoning, and for that reason a total of 6 tablets or 3 suppositories should not be administered more often than every ten days. Because of its action in producing vasoconstriction and affecting damage to blood vessels the drug is contraindicated in coronary-artery and peripheral vascular diseases. Owing to its hypertensive effect, it should not be used when an associated hypertension exists. It is also contraindicated in pregnancy because of its direct stimulating action on uterine musculature. There is some evidence that increased sensitivity to ergot alkaloids may accompany febrile and septic states, hyperthyroidism and disease of the liver or kidneys, and its use is therefore precluded in these conditions. The dosage of caffeine included in this preparation is below the toxic level of 10 gm, and untoward reactions are usually not produced with doses under 1 gm. The side effects of caffeine, which are usually referable to the central nervous and circulatory systems, consist of insomnia, restlessness, excitement, tachycardia, extrasystoles and diuresis. These are usually well controlled by short-acting drugs of the barbiturate series.

SUMMARY

A series of 50 patients with chronic vascular headache were given a therapeutic trial with Cafergone, a new preparation containing a combination of ergotamine tartrate and caffeine.

The data presented suggest that the synergistic action of caffeine when added to ergotamine tartrate is more effective in some patients with migraine than ergotamine alone, when given orally, and is occasionally as effective as ergotamine tartrate when administered hypodermically.

The indications and contraindications for its use and the side actions produced are essentially those of ergotamine tartrate.

The pharmacology of ergotamine and caffeine, their therapeutic actions in the symptomatic treatment of migraine and the treatment of side effects produced are discussed.

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MYCETOMA*

Report of a Case of Actinomycotic Variety

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MYCETOMA is a chronic granulomatous infection usually involving the feet, rarely affecting the hands¹ and still more uncommonly the leg, knee, neck, and trunk.² It is caused by a number of fungi, although the clinical and pathological picture is much the same regardless of etiologic agent. The disease most commonly occurs in males of the working age group with an agricultural background.³ There is no definite racial susceptibility, although certain racial groups, because of their occupational capabilities, are more frequently afflicted.

Mycetoma, or Madura foot, if one uses the geographicoanatomic nomenclature, is most prevalent in the warmer climes. The original reports were from India, but since then numerous cases have been reported from Africa, Europe and South and Central America and certain portions of North America. The majority of the cases in the United States involved people indigenous to the Southern and Western areas. No reports of the occurrence of the condition in Australia have been found.

NOMENCLATURE

According to Castellani and Chalmers,⁴ natives of Ballary knew Madura foot as "ghootloo mahdee" or "eggs of insects" because of the resemblance of the tubercular irregularities on the surface of the foot to ovum.

The vernacular terms "keereenagoah" and "kirinigras" are used in the Punjab and Rajputana respectively to describe mycetoma. Both words mean "dwelling house of worms" and came into use because the sinus tracts were considered to resemble cavities often occupied by larvae of flies.

Other local Indian terms are "slipada" (Bengalese) and "hatty-ka-poung" (Deccan) applicable to both elephantiasis and mycetoma and meaning "elephant leg."⁵

Some descriptive terms used to delineate the condition are endemic degeneration of the bones of the foot, elephant foot, eggfoot, ulcer grave, podalcoma and morbus pedis entophyticus.⁶ The eponym Ballingall's disease, synonymous with mycetoma, persists in the literature.

HISTORY

Madura foot was first noted by Indian physicians and is elucidated in early Sanskrit medical works. By many Kämpfer,⁶ a Pondichery missionary, is credited with being the first to describe the condition. In 1712 he used the term "perical," which means "leg of an elephant" and is applicable to any enlargement of the foot, but his description of the condition is classic for mycetoma. There is, however, some doubt about other very early cases because of laxness of terminology.

Madura foot was frequently misdiagnosed as tuberculosis by early authors. Godfrey,⁷ in 1844, described a probable case of mycetoma as "morbus tuberculosis pedis," believing it to be tuberculosis of the foot with incidental black deposits.

In 1842 Gill in the dispensary of Madura, a city in the southern part of the Madras province of India, called attention to a peculiar affection of the foot. It remained for Colebrook,⁸ Gill's successor, to introduce the term "Madura foot" into the literature in 1846.

In 1860 Van Dyke Carter⁸ established the fungous nature of the disease and proposed the name mycetoma ($\mu\upsilon\kappa\eta\varsigma$, fungus, and $\omega\mu\alpha$, tumor). He also proposed the earliest classification of the disease based on the color of the grains.

Reports have been numerous since that time, especially in the literature of nations founding empires, describing cases found in tropical and subtropical colonies. In 1894 Vincent,⁹ in Algiers, isolated an actinomycete from ochroid grains. In 1898 Wright,¹⁰ of Boston, isolated a hyphomycete from the black-grained variety. In 1906 Brumpt¹¹ reviewed the literature and provided an important mycologic study on the subject.

About that time much work was done in the analysis and classification of the causative organ-

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isms In 1913 Pinoy¹² proposed that cases of Madura foot caused by an Actinomyces be called actinomycoses and those caused by a true mold be designated mycetomas This suggestion was modified by Chalmers,⁷ who, in 1916, used the term mycetoma as synonymous with Madura foot and distinguished actinomycotic and maduromycotic varieties of mycetoma This is the nomenclature accepted today

Mycetoma has been recognized in the United States since 1876, when Kemper and Jameson¹³ reported a case in a resident of Indiana, though some question of the accuracy of the diagnosis has been raised Hyde and Senn,¹⁴ in 1896, reported a case in an Iowa dental student

Since that time a number of cases have been recorded in the literature as having originated in the

is associated with the development of sinuses into the deeper tissues

On section of the involved member a profusion of scarring, discoloration and necrosis is noted Sinus tracts extend to involve any or all of the deeper tissues Abscesses connecting with the sinus tracts may extend along the tendons In advanced cases involvement of osseous tissue is usually present.

Microscopically the fungous grains are seen to be surrounded by polymorphonuclear leukocytes, many of which are undergoing degeneration Lymphocytes, plasma cells and macrophages are present as one proceeds peripherally Varying amounts of fibrous tissue are present An accumulation of large numbers of lipid-bearing macrophages is described in some specimens Eosinophils and pigment-bearing macrophages are also observed

MYCOLOGY

In earlier considerations of Madura foot the disease was usually classified on the basis of the color of the grain found in a given specimen Thus, a pale or ochroid variety, a melanoid variety and an uncommon, red variety were distinguished On microscopical examination the granules were seen to be composed of mycelia, pigment granules and leukocytes

However, it has been shown that each color may be produced by a number of different fungi and that a given species may produce grains of different color⁹

On microscopical examination of the grains, after softening in potassium hydroxide, individual hyphae may be studied

In the maduromycoses the grain is seen to be composed of a central mass of segmented branched hyphae with well defined walls and chlamydospores of various sizes About the periphery the hyphae assume a radiating appearance and terminate in chlamydospores

Grains from the actinomycotic variety are seen to be composed of a mass of more delicate, thin-walled, nonsegmented hyphal filaments Chlamydospores are absent The ends of the hyphae are surrounded by a gelatinous sheath, which gives a club-shaped appearance to the ends of the filaments

Cultural characteristics vary with the causative agent Sabouraud's agar produces the most satisfactory growth Animal inoculations have been tried by numerous authors^{9 12 42 43} On the whole, these have been unsatisfactory, although local, nonprogressive lesions have been produced

Gammel,⁹ in his study on the etiology of the mycetomes in the United States listed thirteen species of the genus Actinomyces as well as nineteen species belonging to two classes (*Fungi imperfecti* and Ascomycetes) and eight genera His list has been modified and brought up to date by Conant⁴⁴

TABLE 1 Cases of Mycetoma Originating in the United States

CASE No.	AUTHOR	LOCATION
1	Kemper and Jameson ¹³	Indiana
2	Hyde et al. ¹⁴	Iowa
3	Pope and Lamb ¹⁵	Texas
4	Wright ¹⁶	Massachusetts
5	Arwice and Lamb ¹⁵	Texas
6	Allison ¹⁷	Texas
7 and 8	Sutton ¹⁸	Texas (2 cases)
9	Winslow ¹⁹	Maryland
10-12	Boyd and Crutchfield ¹	Texas (3 cases)
13	Boyd and Crutchfield ¹	Arizona
14-16	Pagestecher ²⁰	Texas (3 cases)
17-19	Lovejoy and Hammack ²¹	California (3 cases)
20	Lovejoy and Hammack ²¹	Arizona
21	Gammel et al. ⁹	Ohio
22	Harrold ²²	Georgia
23	Halloran ²³	California
24	Thompson and Ideda ²⁴	Minnesota
25	Preston ²⁵	Wisconsin
26	Gay and Bigelow ²⁶	Massachusetts
27	Jones and Aldea ²⁷	Georgia
28-30	Broddley and Howell ²⁸	Texas (3 cases)
31	Gellman and Gammel ²⁹	Maryland
32	Shaw and MacGregor ³⁰	Kansas
33	Hanan and Zoretz ³¹	New York
34	Dixon ³²	Virginia
35	Beck ³³	Indiana
36	Fienberg ³⁴	Georgia
37	Symmers and Sporer ³⁵	New York
38, 39	Gottlieb ³⁶	California (2 cases)
40	Veoble and Gaston ³⁷	Georgia
41-43	Burns et al. ³⁸	Louisiana (3 cases)
44	Wood ³⁹	California
45	Clough ⁴⁰	California
46	Leven (Cited by Clough ⁴⁰)	Texas
47, 48	Fite (Cited by Clough ⁴⁰)	Oklahoma (2 cases)
49	Twining et al. ⁴¹	Pennsylvania

continental United States (Table 1) Over half these have been reported from Texas, California and Arizona

PATHOLOGY

Most commonly the lesion involves the foot Much less often the hands or other portions of the body are affected Characteristically, the disease remains localized to the extremity, although local tissue destruction may be far advanced

The afflicted member is markedly swollen, the amount of swelling corresponding to the progress of the infection Necrosis of the overlying skin

DIAGNOSIS

The diagnosis of mycetoma is not a difficult accomplishment if the condition is kept in mind. A fairly typical set of symptoms and physical findings is present in most cases.

The patient is usually a male of the working age group with an agricultural background and an antipathy toward wearing shoes. There is usually a history of trauma, perhaps slight and far removed in time. A local lesion, either nodular, vesicular, pustular or ulcerative, appears. This is slow to heal, but since it causes little pain, the patient does not seek medical advice. The lesion drains sero-sanguinous or purulent fluid for a time and then heals, at least externally, only to return again at a later date. The involved extremity continues to swell. The condition is for a long time annoying rather than disabling, but it is always progressive.

After several months, perhaps several years, the patient presents himself to a physician.

The patient is by this time in fair general condition, perhaps evidencing some weight loss. Temperature and pulse are within normal limits. There is swelling that involves a large part or all of his foot. The surface of the swelling is marked with nodular, sinus-tract openings and ulcerations. Scar tissue is present, and there may be pigmentary changes. A probe can be inserted through the sinus tracts into the deeper tissues.

The blood count is usually normal, though a mild secondary anemia may be present. If granules are present in the drainage from the sinuses, direct examination under the microscope, as well as culture on appropriate mediums, is very helpful in establishing the fungal origin of the disease. If granules are not so readily available, a biopsy specimen may be taken for histologic examination and for culture.

X-ray study is helpful in establishing the presence of bone involvement. When such involvement is present the picture is that of marked osseous degeneration of both infectious and osteoporotic nature.

DIFFERENTIAL DIAGNOSIS

Tuberculosis can produce local lesions quite similar to those seen in mycetoma. However, systemic symptoms are usually more marked with tuberculosis. In tuberculosis a pulmonary lesion may be present. Tuberculin skin test and culture and guinea-pig inoculation of suppurative material would be helpful in the differentiation from tuberculosis.

Syphilis should be differentiated. Here the history, serologic changes and response to treatment help elucidate the true nature of the condition.

Diabetes can produce a strikingly similar picture, and again the laboratory will aid in diagnosis with tests for hyperglucosuria and hyperglycemia.

The possibility of other fungous diseases such as coccidioidomycosis, blastomycosis and sporotrichosis should be entertained in occasional cases. These should be distinguished by serologic methods, skin tests and identification of the fungus if the clinical picture is not sufficiently clear cut.

The differentiation of Madura foot from yaws and elephantiasis might cause some confusion. Yaws, however, is characterized by a greater systemic response, the occurrence of secondary lesions and the presence of rather definite racial predisposition. Elephantiasis is a lymphangitis involving usually an entire extremity rather than a peripheral portion of one as in mycetoma. Mycologic studies would rule out both these possibilities.

Malignant neoplasm could present a similar local picture. This can be readily separated by mycologic study and biopsy.

TREATMENT

To date no satisfactory therapeutic agent, except surgery, has been devised for the treatment of mycetoma, although numerous ones for both local and systemic use have been tried.

Local application of iodides was advised by Woolrabe⁴⁵. Audrain⁴⁶ suggested mercurochrome. Numerous other local germicides have been tried without favorable results. Chemical or thermal cauterization likewise has been unsuccessful. Tyrothrycin and gramicidin were used in the case reported below.

A long list of medications for internal use has been advocated. Woolrabe⁴⁵ recommended oral administration of iodides. Palmer⁴⁷ advised bismuth, sodium tartrate and copper citrate, reporting good results with this combination. Thymol⁴⁸ and oil of cinnamon⁹ have been suggested, but little success has followed their use. Arspenamine⁴⁹ has not been effective. Sodium propionate has been shown to be effective in vitro in large concentrations, but its clinical use⁴⁸ has not been successful. The sulfonamides have been credited with cures of the actinomycotic variety.^{48, 49} More recently, penicillin has been advocated⁵¹ and streptomycin was used in the case presented here. It is felt by many that the chief effect of these last three agents is on the secondary invaders.

X-ray therapy has been tried⁵² but does little more than slow the progress of the disease.

Amputation or surgical excision is the treatment of choice at this time although a trial of less radical therapy is always indicated.

Prognosis, so far as life is concerned, is good without treatment. Patients have lived for more than fifteen years with the disease without treatment. Prognosis for the cure of the lesion without treatment is extremely poor. An insidious, progressive course with remissions and exacerbations is the rule.

CASE REPORT

W. M., a 51-year-old Negro veteran was admitted to the Lake City Veterans Administration Hospital on May 20, 1947, complaining of swelling of the left foot ulceration and constant pain. About August, 1946, he had first noticed what he called "athlete's foot of both feet" more severe on the left side. By December the symptoms had become very severe, and the patient was plagued by almost continual itching. He believed that he had probably scratched it in his sleep. His physician advised topical medications to the foot. By March the patient was unable to work. He went to bed and remained there continuing to apply local medications to the foot. The skin broke down and numerous small sinus tracts appeared exuding a foul-smelling purulent material. The skin of most of the dorsum of the foot sloughed away and the tendons became visible beneath the necrotic ulcer base. The patient stated that when he lay in bed he could find relief from nagging pain in his foot only by placing a pillow beneath his knee. This was responsible for a 25° permanent deformity of the knee existing at admission.

The patient had always worked as a janitor except for 12 months in the Army as cook's helper. There was no history of agricultural employment. He had never left the state of Florida. There was no history of venereal disease. No history of injury to the foot could be elicited. The patient had lost 15 pounds in weight. There was no history of right sinusitis. There was a history of shortness of breath on exertion. The only peripheral edema had been in his left foot present since December 1946.

Physical examination disclosed a well developed man, mildly undernourished, lying in bed with his left knee extended to 155° with a pillow beneath it. The peripheral vessels were firm but both dorsalis pedis pulses were obtainable as were the posterior tibials. The radial pulse was of good quality. The reflexes were normal except the ankle reflex on the left, which was somewhat diminished probably because of local edema. Examination of the right foot revealed some hypertrophy of the nails but no evidence of onychomycosis. The left foot (Fig. 1) presented a rather bulbous and formless shape from the malleoli to the ends of the phalanges. The left great toe was black and the pulp of the toe diminished in quantity. The left foot presented a large sloughing area, which started over the fourth metatarsal bone on the anterior surface extending to the ankle joint and thence around the apex of the arch on to the plantar surface of the foot beneath the great toe terminating in the region of the third metatarsal head. The skin of the anterior surface was pockmarked with crypts and sinuses. Some eroded areas were evident in which a probe could be inserted into necrotic tissue.

The blood pressure was 140/80.

Urine analysis was negative. Examination of the blood showed a red-cell count of 4,200,000 and a white-cell count of 12,000, with 80 per cent neutrophils and 20 per cent lymphocytes. The nonprotein nitrogen was 25 mg per 100 cc. The fasting blood sugar was 70 mg per 100 cc. A 5-hour glucose tolerance test revealed a normal curve. The blood calcium was 9 mg per 100 cc. A Congo-red test showed no evidence of amyloid disease. The total protein was 5.6 gm per 100 cc. The serologic test for syphilis was negative. The icteric index was 4 units.

The spinal fluid was normal.

X-ray examination demonstrated sclerotic changes in the femoral arteries above the knees. Examination of both legs showed a moderate degree of osteoporosis involving practically the entire left tibia with some involvement of the bones of the right foot. Irregular bone absorption was noted in the cortex at the medial aspect at the left tibia. Films of the left foot showed a marked degree of osteolysis of the first metatarsal bone and the phalanges of the great toe. Osteolytic changes were present to a lesser degree in the other toes.

On admission to the hospital a course of penicillin, 50,000 units every 5 hours was begun. This treatment was continued for a period of 2 months supplemented by administration of sulfadiazine, 1 gm every 4 hours, and Lugol's solution, 15 drops three times a day. The patient was also given a course of Euadin. He was given a therapeutic trial of streptomycin, 0.5 gm every 12 hours for 5 weeks. This was discontinued because of mild deafness and tinnitus and after 7 days a second course was instituted. In 6 weeks symptoms of toxicity reappeared, and the drug was stopped. Neither

symptomatic nor clinical relief of the condition was evident at the time of cessation of treatment.

The patient required codeine and aspirin for relief of the pain in the foot. He was given a high-protein, high-vitamin diet supplemented by intravenous injection of proteins, and was also given a transfusion of 500 cc of whole blood on two occasions.

The treatment consisted of immersion in potassium permanganate soaks for a period of 3 weeks. This was followed by streptomycin and gramicidin by continuous drip. These applications had no apparent effect on the course of the disease.

Cultures were taken from the sinuses and from the necrotic areas on the dorsum and plantar surface of the foot. These were repeatedly grown *Aspergillus niger*. A biopsy was taken. This tissue was examined microscopically and cultured. Culture of the biopsy material again grew *A. niger*. A biopsy specimen was inoculated into a guinea pig and the animal was killed at the end of 4 months. No disease was found on post-mortem examination of the animal. The typical diagnosis of the biopsy specimen was *Madura* probably of the actinomycotic variety. At no time was



FIGURE 1 Left Foot Prior to Amputation

Actinomycetes cultured although repeated attempts were made.

The patient and two controls were tested with a vaccine prepared from *A. niger* cultured from the patient's foot. Controls were negative in 12 and 48 hours. A macule 2 cm in diameter at 12 hours developed and widened to 4 cm in 24 hours. A papule formed in the center and went on to pustule formation 15 cm in diameter. The reaction continued to necrosis and healing. A skin test with purified protein derivative No. 1 was read as 1-cm wheal and 2-cm erythema. Coccidioidin, histoplasmin and blastomycin skin tests were negative, as were agglutinations for typhoid and brucellosis.

On August 27, after no clinical improvement, a decision was made to amputate the left foot, giving the patient a below-the-knee stump. The amputation was satisfactory for a period of about 3 weeks. The patient had a flexion contracture of the left knee at 155°, which was corrected by Kirschner-wire traction to 170°. At the end of 3 weeks an intractable breakdown of the skin at the end of the stump occurred. The erosion continued into the remainder of the gastrocnemius and soleus muscles. A culture showed *A. niger* and *Staphylococcus aureus* coagulase negative. Decision was made to reamputate in the region of the thigh. This was accomplished on October 30. The patient's recovery from that date was uneventful. The stump was normal, and a prosthesis was ordered and provided.

Since the time of the second amputation the patient has continued to gain weight and to improve generally in clinical appearance.

At the first operation the left foot and leg were amputated at the junction of the upper and middle thirds. The foot had a bulbous form. The great toe was black and soft. On the anterior aspect of the foot there was a large ulcerated area, which started over the fourth metatarsal bone and extended

anteriorly upward to the level of the ankle and around the arch to the plantar surface of the foot beneath the great toe, extending as far laterally as the region of the third metatarsal. The skin and ulcer base of the dorsum were marked with sinus openings. The edge of the ulcer was firm, white and undermined. On cut section the process of tissue destruction was seen to have extended to involve the bones of



FIGURE 2 Photomicrograph of the Actinomycotic Abscess (x100)

the foot. The bones distal to and including the metatarsals were softened and eroded. The sinus tracts were seen to be processes of abscess pockets filled with a yellow-green purulent exudate. There was a tendency for the abscesses to extend along the tendon sheath. The muscles in the region of tissue destruction were scarcely recognizable and even



FIGURE 3 Photomicrograph of the Actinomycotic Abscess (x440)

above this point were pale and flabby. The arteries were patent.

The microscopical sections were prepared from the region of the ulcer edge as well as from the site of deeper tissue destruction. Sections of the former showed Negroid skin terminating abruptly at the edge of an ulcer. There a fibrino-purulent exudate covered a granulation-tissue base.

Sections through the deeper tissues showed edematous, degenerating, striated muscle and much granulation tissue.

Numerous small abscesses were present (Fig. 2). These contained a polymorphonuclear exudate. Some of these abscesses were seen to contain granules made up of a thin, delicate mycelium (Fig. 3).

Dr. Norman Conant, of Duke University School of Medicine, was kind enough to review the slides. It was his opinion that they contained actinomycotic granules.

At the second operation the upper third of the left leg and the lower quarter of the left thigh were amputated. An ulcer, 4.0 by 1.0 cm, was situated posterior to the line of the old surgical incision. There was another ulcer, which measured 5.2 by 2.3 cm, over the tibia anteriorly. The ulcer edges were composed of hyaline material and were well demarcated, averaging about 2 mm in thickness. The base of the ulcer was composed of a thin layer of green, purulent material overlying fresh granulation tissue. The ulcer over the tibia was separated from it by a thin layer of periosteum. The muscles were of a tan color and flabby consistence. The arteries were patent. The knee joint when opened presented no abnormality. The distal ends of the remainder of the tibia and fibula were softened and eroded. They were in contact with the purulent exudate from the ulcer near the old incision.

The microscopical sections showed degenerative changes identical with those described for the previous specimen except that no granules were noted.

DISCUSSION

The case of mycetoma reported above followed a rather usual clinical pattern, the response to therapy being similar to that reported in previous cases. Iodides, Fuadin, sulfadiazine, penicillin and streptomycin were tried, with no apparent benefit. Local applications, including potassium permanganate, tyrothricin and gramicidin, did not appreciably alter the course of the infection. Finally, after an adequate surgical operation, the patient made an uneventful recovery.

Of interest is the patient's sensitivity to an extract of *A. niger*. The organism was repeatedly grown on culture from the infected area but was never seen in tissue sections. It is believed that this organism may have been growing in the superficial layers, perhaps as a secondary invader, and that the patient thus became sensitized to the fungus. Unfortunately, we were unable to culture an Actinomycete to check the patient's sensitivity to that organism.

SUMMARY

A case of mycetoma, probably of the actinomycotic variety, is presented.

Of interest is the fact that sensitivity to an extract of *Aspergillus niger* was demonstrated.

Various therapeutic agents, including iodides, Fuadin, sulfadiazine, penicillin and streptomycin, were used, without benefit to the patient. Local applications of potassium permanganate, tyrothricin and gramicidin likewise were of no appreciable aid.

An uneventful recovery followed adequate surgical amputation.

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CLINICAL NOTE

HERPES GESTATIONIS*

Fetal-Anomaly Syndrome Treated
Successfully with Sulfapyridine

JOHN GODWIN DOWNING, M D,† AND
OTIS F JILLSON M D ‡

BOSTON

THE following case is presented to demonstrate the dramatic response of herpes gestationis to small doses of sulfapyridine

ED, a 41-year-old woman, developed herpes gestationis at 4½ months of her second pregnancy. Her first child had died a few days after birth of what was thought to be congenital heart disease. Local applications and antihistamines were of no value. She was given sulfapyridine, 1 gm every 4 hours, and within 4 hours experienced extreme itching, nausea and vertigo. The medication was discontinued, but reinstituted 24 hours later in a dosage of 0.5 gm three times a day. At the end of 3 weeks the skin was entirely clear. Twice the sulfapyridine was stopped and the dermatitis reappeared (Fig 1). On reinstitution of 0.5 gm three times a day the eruption again completely cleared, and the patient was delivered of a normal 8-pound boy.

Lewis¹ reported a similar response to small amounts of sulfathiazole. Intensification of the dermatitis was noted by Mueller and Lapp,² who employed full medical dosage of sulfapyridine. It is suggested that with lower dosage this disease can be controlled with fewer untoward reactions.

In a statistical review of 20 cases of herpes gestationis appearing in 13 women, the average time of onset was five and three-tenths months of pregnancy. Eight of these women had histories of fetal anomalies. It was observed that if the fetal anomaly was a spontaneous abortion there was no associated herpes gestationis, because the uterus was emptied before the stage of pregnancy in which this disease had its onset. It might be postulated

that some cases of spontaneous abortion of unknown etiology are due to this syndrome of fetal anomalies and herpes gestationis. Only if these patients had future pregnancies extending beyond the period



FIGURE 1 Photograph Showing the Generalized Eruption, Consisting Mostly of Patches of Grouped Vesicles and Bullous Lesions, Which Dried Rapidly and Formed Crusts

of gestation in which herpes gestationis has its onset could the diagnosis of the disease be made

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MEDICAL PROGRESS

RH AND OTHER BLOOD GROUPS (Concluded)*

LOUIS K. DIAMOND, M.D.,† AND FRED H. ALLEN, JR., M.D.‡

BOSTON

LABORATORY PROCEDURES IN BLOOD GROUPING

It must be emphasized at the outset that blood-grouping procedures are at present in an *imperfect state of development*. The tests are still dependent in all routine work on the phenomenon of red-cell agglutination. Although this is an extremely sensitive method, as many biologic tests are, it is somewhat unpredictable, being dependent on certain physicochemical and biologic factors. Red cells must be well preserved in serum or in the clot and relatively fresh (one to three days old is best although adequate preservation for several weeks is possible with respect to some of the antigens). The temperature, pH and concentrations of salt and protein must be controlled. Since the antibodies used for typing reagents may vary considerably in their activity (as pointed out in the discussion of anti-D) the conditions must be correct for the activity of the particular antibody. There is no one universally applicable technic.

In performance of blood-grouping tests it is imperative to follow in detail the directions furnished with the typing serum by the manufacturer. The importance of this statement cannot be over-emphasized. The following procedures are applicable in general but must be modified to conform to the directions furnished with a typing serum.⁵⁻⁸

Reagents Required for Blood Grouping and Compatibility Tests

Suspensions of red cells The following suspensions of red cells are required

Red cells, 2 per cent by volume suspended in physiologic saline solution, are used in the tube method for determination of the ABO group and the *tube method* for the compatibility test but should not be used in the slide test.

Red cells, 40 to 50 per cent by volume suspended in plasma or serum, are required in the slide method for determination of the Rh group and the slide method for the compatibility test.

The 2 per cent suspension of red cells can be made by the addition of 1 drop or more of blood for each 1 cc of fresh, uncontaminated, physiologic saline solution. If the patient is anemic, several drops of blood are required to obtain a 2 per cent suspension. Red cells may be obtained from the following sources: capillary whole blood⁹, blood containing an anticoagulant, and clotted blood, by removal of serum containing red cells, or by separation of a fragment of the clot with a wooden applicator stick and agitation in a tube containing physiologic saline solution.

Fluid blood with a hematocrit of 40 to 60 per cent may be obtained from a sample that is clotted or one containing an anticoagulant. If there is anemia, the sample is concentrated by removal of plasma or serum to adjust the hematocrit approximately to 40 or 50 per cent.

Precautions Red cells suspended in saline solution may lose their specific agglutinability during storage in the ice box and should not be relied upon after about twenty-four hours. In clotted blood, stored in the ice box, the red cells retain their agglutinability for many days.

Serums for grouping of blood and for compatibility tests The following serums are required: anti-A and anti-B grouping serums, anti-D grouping serum for the *slide method*¹⁰, serum from recipient and donor for the compatibility tests.

Anti-A and anti-B grouping serums are usually obtained from human donors of blood Groups B and A, respectively. Donors are selected that are known to have high concentrations of the isoagglutinin required. These serums are routinely used in the fluid state. Anti-A and anti-B grouping serums may also be prepared by immunization of rabbits; the serums are dried and used in powdered form¹¹. Anti-D grouping serum is obtained from immune human donors, since serums obtained by immunization of animals do not give consistent or reliable results. Serums

*Adapted from *A Syllabus of Laboratory Examinations in Clinical Diagnosis*. Printed by permission of the Harvard University Press.
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⁹Occasionally a small fibrin clot forms in the suspension. The suspended cells can be washed by centrifugation and resuspended in physiologic saline solution. The fibrin may be removed with a wooden applicator stick.

¹⁰The determination of Rh type can be done by the Landsteiner tube test, if proper saline-agglutinating serum (anti D) is available. It is particularly important, when such a serum is used to follow exactly the directions of the manufacturer.

¹¹Details of this technic are not discussed here.

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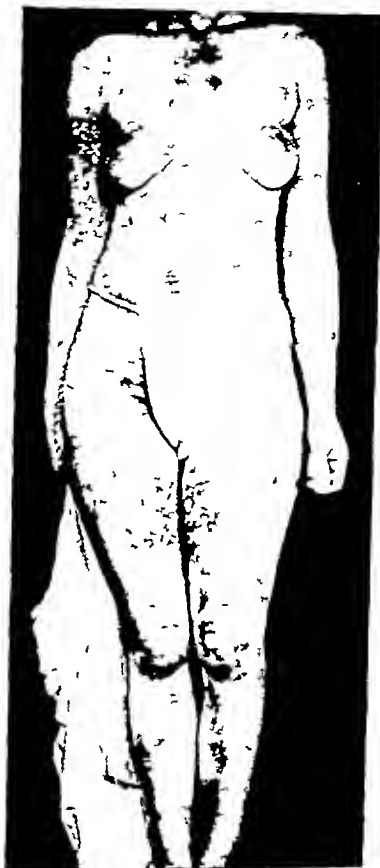


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The 2 per cent suspension of red cells can be made by the addition of 1 drop or more of blood for each 1 cc. of fresh, uncontaminated, physiologic saline solution. If the patient is anemic, several drops of blood are required to obtain a 2 per cent suspension. Red cells may be obtained from the following sources: capillary whole blood⁹, blood containing an anticoagulant, and clotted blood, by removal of serum containing red cells, or by separation of a fragment of the clot with a wooden applicator stick and agitation in a tube containing physiologic saline solution.

Fluid blood with a hematocrit of 40 to 60 per cent may be obtained from a sample that is clotted or one containing an anticoagulant. If there is anemia, the sample is concentrated by removal of plasma or serum to adjust the hematocrit approximately to 40 or 50 per cent.

Precautions Red cells suspended in saline solution may lose their specific agglutinability during storage in the ice box and should not be relied upon after about twenty-four hours. In clotted blood, stored in the ice box, the red cells retain their agglutinability for many days.

Serums for grouping of blood and for compatibility tests The following serums are required: anti-A and anti-B grouping serums, anti-D grouping serum for the *slide method*¹⁰, serum from recipient and donor for the compatibility tests.

Anti-A and anti-B grouping serums are usually obtained from human donors of blood Groups B and A, respectively. Donors are selected that are known to have high concentrations of the isoagglutinin required. These serums are routinely used in the fluid state. Anti-A and anti-B grouping serums may also be prepared by immunization of rabbits; the serums are dried and used in powdered form.¹¹ Anti-D grouping serum is obtained from immune human donors, since serums obtained by immunization of animals do not give consistent or reliable results. Serums

*Adapted from *A Syllabus of Laboratory Examinations in Clinical Diagnosis*. Printed by permission of the Harvard University Press. From the Blood Grouping Laboratory of Boston and the Children's Medical Center and the Department of Pediatrics, Harvard Medical School.

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‡Instructor in pediatrics, Harvard Medical School, assistant physician, the Children's Medical Center, associate director, Blood Grouping Laboratory of Boston.

⁹Occasionally a small fibrin clot forms in the suspension. The suspended cells can be washed by centrifugation and resuspended in physiologic saline solution. The fibrin may be removed with a wooden applicator stick.

¹⁰The determination of Rh type can be done by the Landsteiner tube test, if proper saline-agglutinating serum (anti-D) is available. It is particularly important when such a serum is used to follow exactly the directions of the manufacturer.

¹¹Details of this technic are not discussed here.

for the compatibility tests are obtained from clotted blood from the recipient and donor Plasma is usually unsatisfactory as a substitute for serum

Precautions Grouping (typing) serums should never be used unless they are proved* to be potent at the time they are used Anti-A and anti-B grouping serums should have a known high agglutination titer, showing strong agglutination of sensitive red cells when diluted to 1 64 or more with physiologic saline solution Serums for the slide test should show a high avidity, as evidenced in producing macroscopic agglutination in one minute, when 1 drop of serum is mixed with 1 drop of cell suspension on a glass slide Liquid grouping serums may be preserved indefinitely in the frozen state and will maintain potency for many months when stored at ice-box temperature provided there is no bacterial contamination Plasma should not be used in the compatibility tests since it contains fibrinogen and produces rouleaux formation as observed microscopically

Determination of ABO Blood Groups

Principle The first step in the preparation for blood transfusion is to determine the ABO blood group of the recipient and of the donors, at least the first step of the following three procedures being used anti-A and anti-B grouping serums of known potency are always used to determine the blood group of unknown red cells, the blood group, especially of Group O, may be confirmed by a test of the unknown serum from the recipient or donor with red cells of known Group A and Group B, the potency of anti-A and anti-B grouping serums may be checked qualitatively and quantitatively by a test with red cells of known Group A₁ and Group B, respectively

For these tests, the *tube method of Landsterner* is recommended as the standard procedure since it is rapid, reliable and simple, has a macroscopic end point of obvious agglutination and permits a large number of tests to be run simultaneously It is superior to the *slide method*, which is not described here The test tube should have an internal diameter of approximately 7 mm Reagents are measured in drops, *separate* capillary pipettes for each of the *grouping serums being used* One pipette, thoroughly rinsed in physiologic saline solution, may be used for the several suspensions of red cells One drop of serum is added to the tube, and then 2 drops of a 2 per cent suspension of red cells The tubes are agitated to mix the reagents, centrifuged† at 500 r p m for one minute, and remixed gently to loosen the cells from the bottom of the tube, and the agglutination is read macroscopically

*The potency of serum is readily checked as described below

†The tubes are not incubated and can be centrifuged immediately

Tubes showing no macroscopic agglutination are read microscopically for agglutination by transfer of a small drop to a glass slide

Method for determination of the ABO blood groups The tests listed in Table 10, by the tube method

TABLE 10 ABO Grouping with the Use of Known Antiserums (Standard Method)

GROUPING SERUM OF KNOWN POTENCY	2 PER CENT SUSPENSION OF RED CELLS TO BE GROUPED
1 drop Anti-A	2 drops
Anti B	2 drops

Interpretation. The interpretation is as follows:
 No agglutination (macroscopic or microscopic) indicates blood Group O
 Agglutination only with anti A serum indicates blood Group A
 Agglutination only with anti B serum indicates blood Group B
 Agglutination with both anti A and anti B serums indicates blood Group AB

of Landsterner, are always required for every blood grouping

Method for confirmation of blood group with the use of unknown serum It is desirable to confirm the blood group by a test of the serum from the recipient or donor as listed in Table 11, red cells of known‡ Groups A₁ and B, preferably from D-negative persons, being used

These particular tests should not replace the standard method of blood grouping described above,

TABLE 11 Typing of Unknown Serum with the Use of Known A₁ and B Cells

UNKNOWN SERUM TO BE TESTED	2 PER CENT SUSPENSION OF RED CELLS OF KNOWN BLOOD GROUP
1 drop 1 drop	2 drops Group A ₁ Group B

Interpretation. The interpretation is as follows for the blood group of the unknown serum:
 Agglutination* of both Group A₁ and Group B cells indicates blood Group O
 Agglutination* of Group A₁ cells only indicates blood Group B
 Agglutination* of Group B cells only indicates blood Group A
 No agglutination (macroscopic or microscopic) and no hemolysis indicates blood Group AB

*Occasionally, hemolysis occurs. When specific hemolysis is equivalent to agglutination but may be caused, nonspecifically by bacterial or chemical contamination or by improperly cleaned test tubes

since the agglutinins in serums from unknown patients are often low in potency, and occasionally absent

Method for checking the potency of grouping serums The grouping serums to be tested can be examined qualitatively as described above in the description of the method for the confirmation of blood group, 2 per cent suspensions of known Group A₁B or Group A₂ and Group B cells, respectively, being

‡Physicians and laboratory personnel are advised to determine and record their blood groups for ABO and Rh to make available at all times red cells of known groups for laboratory tests. The donors of these A and B test cells should be Rh negative (cde/cde) if possible and the donor of A cells should be of the subgroup A₁

used. The potency of grouping serums can be tested *quantitatively* by a preparation of serial dilutions of 1 10 to 1 160 or higher and the addition of equal quantities of a 2 per cent suspension of agglutinable red cells from Group A₂ or Group B. The maximum dilution of the serum that produces macroscopic agglutination of an equal quantity of cell suspension is taken as the end point to express the potency or titer of the serum.

False-negative agglutination. A dangerous error in blood grouping results from the failure to obtain agglutination when it should have occurred. The major cause of false-negative agglutination is weakness of the grouping serum.⁶ Another cause is the use of old cells that are not agglutinable because of long standing.⁸ Fluid grouping serum may deteriorate from standing in the room or from bacterial contamination. The most frequent error occurs from the use of anti-A grouping serum of inadequate potency. In this instance, no agglutination may occur with blood of Group A₁, and the blood group may be reported erroneously as Group O or B. This has occurred.²⁴ Such blood, when given to a Group O recipient has resulted in a fatal hemolytic transfusion reaction. Bloods of Group A₂ and Group A₂B are particularly subject to false-negative reactions since the antigen A₂ is significantly less agglutinable than the antigen A₁. A potent anti-A grouping serum will agglutinate red cells of Group A₁ and A₂ as well as A₁B and A₂B. A weak anti-A typing serum may fail to agglutinate A₂ cells. It is not necessary in the clinical use of transfusions to determine the subgroups of Group A, but it is obligatory that the anti-A typing serum be potent enough to agglutinate the subgroups of Group A. In addition, the compatibility test cannot be relied upon to detect errors arising from weak grouping serums for the following reasons: the agglutinin titer of the serum obtained from most persons tested is lower than that of a proper typing serum, and a false negative compatibility test has resulted²¹ when weak typing serum also failed to produce agglutination.

False-positive agglutination, rouleaux formation and cold agglutinins. False-positive agglutination should be suspected immediately if the major compatibility test by the tube method shows unexpected agglutination and the blood grouping has been checked. If this occurs, the recipient's red-cell suspension should be tested with the recipient's own serum, by means of the same technic as for the major compatibility test. If agglutination occurs in this test, it may be due to rouleaux formation or auto-agglutination and should be analyzed, since this serum may agglutinate all cells tested. Rouleaux formation of varying degree is always seen microscopically when cells are suspended in plasma.²⁵

Plasma should never be used for a compatibility test requiring interpretation by microscopical examination. In serum, rouleaux formation occurs

as the result of hyperglobulinemia. The formation of *rouleaux* is characteristic in its appearance, non-specific in affecting all red cells, nonabsorbable and readily decreased or eliminated by dilution of the serum 1 2 or 1 4 with physiologic saline solution. *Rouleaux formation is not a contraindication to transfusion with the cells tested.*

Cold agglutinins may cause autoagglutination and panagglutination of all cells even at room temperature.²⁶ Red cells from a patient with cold agglutinins may show agglutination with anti-A and anti-B grouping serums owing to adsorbed cold agglutinins and may thus appear to be Group AB. The red cells may be freed of cold agglutinins by washing three or more times in a large volume of warm physiologic saline solution. The cold agglutinins are nonspecific and adsorbable at low temperatures and may cause agglutination at room temperature that is reversed at 37°C. Cold agglutinins are not a contraindication to transfusion. Rarely, auto-agglutinins, other than cold agglutinins, are observed that produce agglutination at temperatures between 4 and 37°C. Occasionally, suspensions of blood infected with bacteria develop a panagglutination.⁸ This complication can be avoided by the use of fresh suspensions of red cells made from uncontaminated blood samples preserved in the icebox. Cold agglutinins found in a person's serum may be specific isoantibodies (anti-M, anti-P, anti-Lewis and so forth) — if so they will fail to agglutinate his own red cells.

Determination of the Rh Blood Group

Principle. For routine transfusion therapy it is essential to determine whether the blood is D-positive (85 per cent of the population) or D-negative (15 per cent of the population). The slide method is recommended since it is rapid and gives a strong macroscopic agglutination that provides a definitive and reliable end point.

Anti-D grouping serum for the slide method cannot be used for cells suspended in saline solution since no agglutination may occur, the cells must be suspended in a protein* medium. This grouping serum is usually labeled anti-Rh (anti-D) grouping serum "for slide test (hyperimmune)." It is a hyperimmune human serum, inactive in saline solution, that contains incomplete antibodies and may contain blocking† antibodies. It produces vigorous agglutination of red cells, in 40 to 50 per cent concentration, that are suspended in protein solutions, such as plasma, serum and albumin.

The anti-D grouping serum is obtained from immunized human donors. The naturally occurring anti-A or anti-B agglutinins in these serums are

*Two per cent by volume of red cells suspended in the patient's own serum or in albumin solution (human or bovine) can be used with this anti Rh serum in the tube method. The important factor is the presence of a sufficient concentration of protein.

†Blocking antibodies will inhibit the agglutination in the test tube of red cells that are mixed with serum known to agglutinate D positive cells. The blocking phenomenon has not been observed with the slide-test technic using a 50 per cent cell suspension in serum or plasma.

adsorbed or neutralized, leaving only the anti-D agglutinin.^{6, 37} Thus, the anti-D grouping serum agglutinates D-positive red cells, but does not agglutinate D-negative red cells, whether of Group O, A, B or AB.

Slide method for Rh grouping³⁸ A 0.2-cc sample of blood, with a hematocrit of 40 to 50 per cent, is transferred to a glass slide. Then 0.1 cc of anti-D grouping serum for the slide method is added. The blood and the typing serum are mixed over an area about 2.5 cm square, with a wooden applicator, the mixture being spread over the whole width of the slide and the ends of the film squared off. The resulting film should not be very heavy, but must not be so thin as to dry too quickly. The mixture is tilted back and forth on an illuminated ground-glass background that is warmed to about 40°C by the heat from an electric bulb. Agglutination is read, *only macroscopically*, after a period of 1 to 3 minutes of occasional tilting. The result should be compared to known D-positive and D-negative bloods set up in the same manner. Tests must be read *before drying* since a negative test may appear quite granular when dry. If drying occurs too rapidly for easy performance of the slide test owing to excessive dryness of the air a drop of bovine albumin solution* or of human albumin solution (20 to 25 gm of salt-poor albumin per 100 cc of physiologic saline solution) may be added after the slide has been exposed for thirty to sixty seconds. This addition of albumin usually enhances the agglutination if it is going to occur. Technically, it is advisable to add the drop of albumin to the top edge of the blood mixture while the slide is slightly tilted and to watch the drop as it goes down through the blood mixture before the slide is tilted again. Agglutination, if it is to occur, usually is instantly apparent in and around, and in the wake of, the drop of albumin.

Interpretation The result is reported, the variety of anti-D serum used being stated. If agglutination is observed, it is reported as D-positive. If no agglutination is observed, it is reported as D-negative. It is advisable to use more than one potent anti-D serum. If enough different serums were used in parallel, one would not overlook as many of the irregular, and important but uncommon, D antigens discussed previously. False-negative results may be expected with some regularity in the newborn baby (D-positive) with erythroblastosis fetalis. If the cells of the baby are completely coated with "blocking" antibody from the mother, they may fail to agglutinate in typing serum but may give a strongly positive direct Coombs test. Otherwise, there is no greater difficulty in typing of the blood of the newborn baby than that of an adult, provided the typing serums are potent and

from human sources rather than animal. Carefully obtained samples of blood from the placental end of the umbilical cord are satisfactory for typing purposes.

Compatibility Tests

Compatibility tests are essential to avoid errors in blood grouping, and especially to detect abnormal or immune agglutinins in the serum of the recipient. It is recommended that *three compatibility tests be done before each transfusion*—that is, two by the tube method and one by the slide method.

Tube method By means of the Landsteiner tube method, the compatibility tests shown in Table 12 are set up.

Slide method It has been demonstrated³⁸ that the slide method will detect the presence of hyper-

TABLE 12 *Compatibility Test, Major and Minor, by the Tube Method,* with the Use of Saline Solution*

ORIGIN OF SERUM 1 drop	ORIGIN OF RED CELLS† 2 drops	COMMENT‡
Recipient	Donor	Major compatibility
Donor	Recipient	Minor compatibility

*The tubes are incubated at 37°C for ten or fifteen minutes, centrifuged for one minute at 500 r.p.m. and read.

†Two per cent suspension in saline solution.

‡Lack of agglutination indicates compatibility.

immune anti-Rh isoagglutinins. Thus the slide test serves as a simple test for the detection of dangerous incompatibilities that might cause a fatal hemolytic transfusion reaction. The compatibility test by the tube method usually will not detect the presence of anti-Rh agglutinins since it fails to detect the hyperimmune antibodies. The method is as follows.

A sample of 0.2 cc of the donor's oxalated whole blood, with a hematocrit of 40 to 50 per cent, is transferred to a glass slide and 0.1 cc of serum from the recipient is added as described above. The slide is read only macroscopically. If agglutination occurs, the blood is judged incompatible. Such incompatibility in this test may be due to anti-A or anti-B agglutinins, anti-Rh agglutinins or agglutinins other than anti-Rh. The test is designed primarily to detect hyperimmune anti-Rh agglutinins. A control for comparison is *always necessary*, by the use of 0.1 cc of the donor's serum or plasma, mixed with 0.2 cc of the donor's blood.

Interpretation of compatibility tests The compatibility tests in saline solution serve as a crude check on the accuracy of the determination of the blood group of donor and recipient. Agglutination is reliable evidence of the presence of an agglutinating agent that may be effective in vivo^{39, 40} and

*Supplied by Armour Laboratories, Chicago, Illinois.

may contraindicate the transfusion. A negative result does not necessarily exclude an agglutinin that may produce a hemolytic transfusion reaction^{34, 39}, no agglutination may occur with weak anti-A antibody or hyperimmune Rh antibodies.

The *compatibility test* in a saline-free protein medium (slide test) will usually detect the presence of a hyperimmune antibody that gives no agglutination in a saline medium. This screening test serves (when agglutination occurs) as a major warning that incompatibility exists and that transfusion is contraindicated until the isoantibody is identified.

Even when all cross-match tests described above show no agglutination it is still not certain in all instances that no abnormal antibodies exist in the patient's (or donor's) serum that could cause a transfusion reaction. A list of the isoantibodies that may be encountered in serum is shown in Table 13. The Coombs tests, described below, serve

patients contain isoantibodies that will not produce agglutination of red cells suspended in saline solution, although the antibody will transfer to red cells, coating them. For example, at least three different isoantibodies can be so transferred to normal red cells — namely, the hyperimmune anti-D antibody, the antibody in serums from patients with acquired hemolytic jaundice and the hemolysin from patients with paroxysmal (cold) hemoglobinuria.⁴⁵

Two different methods are available for the detection of antibody on sensitized but unagglutinated red cells: the use of an antihuman globulin serum (the Coombs test⁴⁶) and the addition to saline-free red cells of a solution of albumin or other plasma proteins.^{22, 47} In both tests the production of agglutination in the unagglutinated suspension indicates the presence of antibody on the red cell. The Coombs test is remarkably *sensitive* in the detection of small degrees of sensitization, and it is nonspecific since agglutination occurs with a variety of antibodies. The test with albumin solution is also nonspecific but is less sensitive and may be negative when the Coombs test is strongly positive.

The *value of the Coombs test in blood grouping* is immediately apparent from its sensitivity and nonspecificity in the detection of antibodies already present on red cells or the detection of antibodies that are transferred from serum to normal red cells. Although antibodies may *not* produce agglutination in saline suspensions of red cells they may cause agglutination and a severe hemolytic transfusion reaction *in vivo*, in the transfusion of D-positive red cells into a patient with hyperimmune anti-D isoantibody in the serum. Thus, the Coombs test has an important place in the testing for compatibility in certain instances of isoimmunization.

The Coombs test. Coombs, Mourant and Race,⁴⁶ in 1946, produced an immune antiglobulin serum in rabbits by the repeated injection of human serum or gamma globulin of human serum (not red cells). When this serum was adsorbed by washed normal human cells, it produced no agglutination of normal washed red cells in saline solution but did agglutinate previously unagglutinated suspensions of red cells coated with human isoantibodies. The procedure known as the *direct Coombs test* is performed by the incubation of equal parts of Coombs's serum and of a suspension of red cells washed in saline solution (unknown cells). In the procedure known as the *indirect Coombs test*, a serum is tested for the presence of antibody by incubation, in the serum, of selected normal red cells, the red cells are then washed in saline solution and tested for adsorbed antibody using antiglobulin serum as in the direct Coombs test.

†This is comparable to the slide test methods for detection of D positive cells or of anti D isoantibody, since both procedures avoid the use of saline solution and employ protein rich mediums of plasma or serum.

TABLE 13 *Types of Isoantibodies That Have Been Encountered in Human Serums*

ANTIGENS	NATURAL ANTIBODIES	IMMUNE ANTIBODIES				
	SALINE AGGLUTININS (MOST ACTIVE IN THE COLD)	SALINE AGGLUTINATING	ACTIVE IN SERUM OR PLASMA*	ACTIVE IN ALBUMIN†	DEMONSTRABLE ONLY BY INDIRECT COOMBS TEST	
		37°C				
A B	Universal	+	+	-	-	
O D	+	(rare)	-	-	-	
C E c Cw	0	+	-	+	+	
e d	0	+	-	+	-	
M N	+	(rare)	-	-	-	
S P	0	+	-	-	+	
Lewis	+	+	-	-	-	
Kell	0	+	-	+	+	
k	0	+	-	-	-	
Lutheran	0	+	-	-	-	

*Not in saline solution or albumin

†Not in saline solution

as further methods for testing of compatibility by the detection of antibodies on red cells and in serum.

Coombs Tests and Test with Serum Albumin for Isoantibodies on Red Cells

It has been amply demonstrated that *red cells* may be coated with antibody globulin in certain instances but fail to agglutinate when suspended in saline solution.^{6, 20, 23, 28, 40, 41} This occurs, for example, for D-positive red cells coated with hyperimmune anti-D isoantibody,* as in the erythroblastotic infant. Coating of red cells without agglutination in saline solution or serum has been demonstrated in certain patients with acquired hemolytic jaundice⁴²⁻⁴⁵, in this instance the isoantibody is of unknown origin and is not related to any blood group. Conversely, the *serums* of certain

*The D antigen and antibody are most commonly involved in isoimmunization but other antigens of the CDE system are occasionally the cause of immunization.

Method for direct Coombs test Two drops of a 2 to 4 per cent saline suspension of red cells from the patient to be tested are placed in a small, clean test tube (8 by 70 mm). The tube is filled with uncontaminated saline solution by means of a clean pipette, the saline solution being introduced forcibly to disperse the red cells in the fluid. The tube is centrifuged rapidly for one or two minutes, and the supernatant saline solution is poured off. The cell button is then examined. If gross agglutination of the red cells is present, washing must be continued until spontaneous agglutination has been eliminated. If the cell button resuspends easily without gross clumping, the following steps are performed.

The *washing* is repeated at least twice more, the cell button being shaken up by tapping before the fresh saline solution is added. Extreme precautions about cleanness of glassware and saline solution are necessary to avoid unintentional introduction into the test tube of even minute amounts of human serum, which would be sufficient to neutralize the antiglobulin reagent when added. For the same reason, the tubes should not be inverted for mixing, since such a procedure involves the use of a potentially serum-contaminated finger or cork.

After three or four washings the cells are checked for agglutination and finally resuspended in saline solution to make approximately a 5 per cent suspension. An unagglutinated suspension of red cells is required for the Coombs test since the end point of the test is the presence or absence of agglutination. One or two drops (depending on potency) of Coombs's antiglobulin reagent are added, and mixed by gentle shaking. The tube is allowed to incubate* for thirty to sixty minutes at 37°C, it is then centrifuged at 500 r p m for 1 minute and the cells are examined for agglutination. A "positive test" is evidenced by agglutination of the red cells, which may be a solid agglutinated cell button, lesser degrees of macroscopic agglutination, or only microscopical agglutination. As a control, a tube containing the washed suspension of cells (but no Coombs's reagent) is incubated and should show no agglutination. Agglutination with Coombs's reagent indicates that globulins had been absorbed onto

the red cells and were firmly enough fixed to withstand washing.

Method for indirect Coombs test Two drops of a 2 to 4 per cent suspension of the donor cells in saline solution are mixed with two drops of the recipient's serum in a chemically clean test tube (8 by 70 mm). The mixture is incubated at 37°C for at least thirty minutes, centrifuged at 500 r p m for one minute and examined for agglutination of the red cells. (It should be noted that so far the technic is that of the "major" cross match.) Agglutination at this point concludes the test, since nothing further is to be gained by the Coombs method. If no agglutination is present, the test is completed by performance of the steps described for the direct Coombs test, by the addition of the anti-globulin serum to the donor's washed cells.

Albumin test Red cells suspected of having adsorbed hyperimmune antibodies, which failed to agglutinate them, in saline solution, after incubation at 37°C for thirty to sixty minutes are freed of saline solution after centrifugation and are resuspended in a solution of albumin (human or bovine, 20 gm per 100 cc of physiologic saline solution). Compatible plasma, serum or mixtures of albumin with serum or plasma may also be used. After standing for fifteen minutes, the tubes are centrifuged for one minute at 500 r p m, and the cell button is examined for agglutination. Doubtful or negative reactions are checked microscopically.

Limitations and interpretations A failure of sensitized cells to agglutinate in the Coombs test (false-negative reactions†) may result from weak anti-globulin serum or contamination of the test mixture with serum that may neutralize the Coombs serum. A false-positive agglutination may result from cold autohemagglutinins that were not removed by washing or from poor preparation (incomplete adsorption of nonspecific agglutinins for human red cells) of the Coombs serum. It is imperative that in the performance of the Coombs test, the suspensions be mixed by agitation of the tubes rather than by mixing against the finger, which may be contaminated with protein. Also,

*Some antiglobulin serums are potent enough for centrifugation to be done immediately.

†A control observation should be made to prove the effectiveness of the procedure and of the Coombs serum. This is done by the indirect Coombs test using known D positive red cells and known hyperimmune anti D isogantibody for sensitization. These cells should give no agglutination after washing but should show marked agglutination when treated with Coombs's serum.

glassware and solutions must be chemically and bacteriologically clean.

A *positive direct or indirect Coombs test* (agglutination occurring only after addition of anti globulin serum) or a positive *albumin test* indicates the presence of an antibody on the red cell, but does not indicate the kind or source of the antibody except when anti-D isocombody is suspected or known to be present. In the presence of the anti-D isocombody, transfusion with D-positive cells is contra-indicated. In the presence of a serum antibody in acquired hemolytic jaundice, transfusion is not contra-indicated but the transfused cells may be rapidly sensitized and destroyed *in vivo*.⁴⁷ Positive direct or indirect Coombs tests have generally not been obtained in cases in which immune anti-A or anti-B isocombodies are involved.

Gardner⁴⁸ has confirmed the fact that certain cases with *acquired hemolytic jaundice* show agglutination of the red cells in the direct Coombs test; in these cases the serum contains an antibody that may cause agglutination of normal red cells and a positive indirect Coombs test only when the pH of the serum is adjusted to 6.8.

Identification of Isocombodies

The detection of isocombodies has been discussed. The identification of the isocombodies that may be found in transfusion reactions and in erythroblastosis fetalis cannot be described adequately here, except for the identification of anti-D antibodies (see Tables 4 and 15). In general, an unknown serum is tested for agglutination with red cells from at least 2 D-positive and 2 D-negative Group O subjects. The isocombodies may be 'complete' (giving agglutination in saline solution) or 'incomplete' (hyperimmune) (giving agglutination only in saline-free protein medium), or may be a mixture of both 'complete' and 'incomplete' antibodies. Accordingly, suspensions of red cells are set up both in saline solution and (after removal of the solution) in albumin solution.

The detection of hyperimmune anti-A or anti-B requires special care. Use can be made of Witelsky's⁴⁹ observation that these antibodies are difficult to neutralize with the corresponding specific soluble antigen. A sufficient amount of the dilute solution of A and B substances (0.1 per cent, Sharp and Donahue) usually 1 to 2 parts, is added to the native serum to neutralize, completely or nearly, the saline-

active antibody, as determined by titration in a saline system. This "neutralized" serum can then be tested in a serum system (using for example, serum and cells from a Group A person for the dilution of, and testing of the serum suspected of containing hyperimmune anti-A), by successive dilutions with compatible human serum and the use of a 2 to 4 per cent suspension of known cells in serum. The hyperimmune A and B antibodies are inactive in saline solution and usually also in bovine as well as human albumin. Wiener⁵⁰ has found a buffered solution of acacia useful as a suspension medium. Group A, red cells should be used in the titration of a suspected hyperimmune anti-A, since the titer may be much lower against Group A₂ cells, or even absent, after the addition of the soluble antigen.

Trypsin and Other Agglutinating Enzymes

The use of trypsin in blood-grouping techniques has been reported by Morton and Polesky⁵¹ and studied extensively by others.⁵²⁻⁵⁴ Exposure of normal red cells to a dilute solution of trypsin alters them so that they are immediately agglutinated by hyperimmune (or blocking) antibodies when suspended in saline solution. The use of trypsin or other appropriate enzymes to treat red cells promises to a blood-grouping procedures by great simplification. The exact techniques have not had wide enough trial to be recommended for routine use.

SUMMARY

Seven blood-group systems are described comprising at least 20 separate and specific blood-group antigens. All are of very great importance in the fields of genetics, anthropology and legal medicine. At least 10 have been found responsible for cases of erythroblastosis fetalis. These same 10 have been found responsible for hemolytic transfusion reactions.

Although there is much confusion regarding the blood groups, they are simple enough to understand when considered one by one, which is usually possible in clinical practice. The chief difficulty consists of considerable variability in the types of circulating antibodies, which may occur naturally or may be produced by active immunization against any one of the blood-group antigens. This variability makes necessary, in the present imperfect

Method for direct Coombs test Two drops of a 2 to 4 per cent saline suspension of red cells from the patient to be tested are placed in a small, clean test tube (8 by 70 mm). The tube is filled with uncontaminated saline solution by means of a clean pipette, the saline solution being introduced forcibly to disperse the red cells in the fluid. The tube is centrifuged rapidly for one or two minutes, and the supernatant saline solution is poured off. The cell button is then examined. If gross agglutination of the red cells is present, washing must be continued until spontaneous agglutination has been eliminated. If the cell button resuspends easily without gross clumping, the following steps are performed.

The *washing* is repeated at least twice more, the cell button being shaken up by tapping before the fresh saline solution is added. Extreme precautions about cleanness of glassware and saline solution are necessary to avoid unintentional introduction into the test tube of even minute amounts of human serum, which would be sufficient to neutralize the antiglobulin reagent when added. For the same reason, the tubes should not be inverted for mixing, since such a procedure involves the use of a potentially serum-contaminated finger or cork.

After three or four washings the cells are checked for agglutination and finally resuspended in saline solution to make approximately a 5 per cent suspension. An unagglutinated suspension of red cells is required for the Coombs test since the end point of the test is the presence or absence of agglutination. One or two drops (depending on potency) of Coombs's antiglobulin reagent are added, and mixed by gentle shaking. The tube is allowed to incubate* for thirty to sixty minutes at 37°C, it is then centrifuged at 500 r p m for 1 minute and the cells are examined for agglutination. A "positive test" is evidenced by agglutination of the red cells, which may be a solid agglutinated cell button, lesser degrees of macroscopic agglutination, or only microscopical agglutination. As a control, a tube containing the washed suspension of cells (but no Coombs's reagent) is incubated and should show no agglutination. Agglutination with Coombs's reagent indicates that globulins had been absorbed onto

the red cells and were firmly enough fixed to withstand washing.

Method for indirect Coombs test Two drops of a 2 to 4 per cent suspension of the donor cells in saline solution are mixed with two drops of the recipient's serum in a chemically clean test tube (8 by 70 mm). The mixture is incubated at 37°C for at least thirty minutes, centrifuged at 500 r p m for one minute and examined for agglutination of the red cells. (It should be noted that so far the technic is that of the "major" cross match.) Agglutination at this point concludes the test, since nothing further is to be gained by the Coombs method. If no agglutination is present, the test is completed by performance of the steps described for the direct Coombs test, by the addition of the anti-globulin serum to the donor's washed cells.

Albumin test Red cells suspected of having adsorbed hyperimmune antibodies, which failed to agglutinate them, in saline solution, after incubation at 37°C for thirty to sixty minutes are freed of saline solution after centrifugation and are resuspended in a solution of albumin (human or bovine, 20 gm per 100 cc of physiologic saline solution). Compatible plasma, serum or mixtures of albumin with serum or plasma may also be used. After standing for fifteen minutes, the tubes are centrifuged for one minute at 500 r p m, and the cell button is examined for agglutination. Doubtful or negative reactions are checked microscopically.

Limitations and interpretations A failure of sensitized cells to agglutinate in the Coombs test (false-negative reactions[†]) may result from weak antiglobulin serum or contamination of the test mixture with serum that may neutralize the Coombs serum. A false-positive agglutination may result from cold autohemagglutinins that were not removed by washing or from poor preparation (incomplete adsorption of nonspecific agglutinins for human red cells) of the Coombs serum. It is imperative that in the performance of the Coombs test, the suspensions be mixed by agitation of the tubes rather than by mixing against the finger, which may be contaminated with protein. Also,

*Some antiglobulin serums are potent enough for centrifugation to be done immediately.

[†]A control observation should be made to prove the effectiveness of the procedure and of the Coombs serum. This is done by the indirect Coombs test using known D positive red cells and known hyperimmune anti-D antibody for sensitization. These cells should give no agglutination after washing but should show marked agglutination when treated with Coombs's serum.

glassware and solutions must be chemically and bacteriologically clean

A *positive direct or indirect Coombs test* (agglutination occurring only after addition of antiglobulin serum) or a *positive albumin test* indicates the presence of an antibody on the red cell but does not indicate the kind or source of the antibody except when anti-D isoantibody is suspected or known to be present. In the presence of the anti-D isoantibody transfusion with D-positive cells is contraindicated. In the presence of a serum antibody in acquired hemolytic jaundice, transfusion is *not* contraindicated but the transfused cells may be rapidly sensitized and destroyed *in vivo*.⁴³ Positive direct or indirect Coombs tests have generally not been obtained in cases in which immune anti-A or anti-B isoantibodies are involved.

Gardner⁴⁴ has confirmed the fact that certain cases with *acquired hemolytic jaundice* show agglutination of the red cells in the direct Coombs test, in these cases the serum contains an antibody that may cause agglutination of normal red cells and a positive indirect Coombs test only when the pH of the serum is adjusted to 6.8.

Identification of Isoantibodies

The detection of isoantibodies has been discussed. The identification of the isoantibodies that may be found in transfusion reactions and in erythroblastosis fetalis cannot be described adequately here, except for the identification of anti-D antibodies (see Tables 4 and 13). In general, an unknown serum is tested for agglutination with red cells from at least 2 D-positive and 2 D-negative Group O subjects. The isoantibodies may be "complete" (giving agglutination in saline solution) or "incomplete" (hyperimmune) (giving agglutination only in saline-free protein medium) or may be a mixture of both "complete" and "incomplete" antibodies. Accordingly suspensions of red cells are set up both in saline solution and (after removal of the solution) in albumin solution.

The detection of hyperimmune anti-A or anti-B requires special care. Use can be made of Witelsky's⁴⁵ observation that these antibodies are difficult to neutralize with the corresponding specific soluble antigen. A sufficient amount of the dilute solution of A and B substances (0.1 per cent, Sharp and Dohme), usually 1 to 2 parts, is added to the native serum to neutralize, completely or nearly, the saline-

active antibody as determined by titration in a saline system. This "neutralized" serum can then be tested in a serum system (using, for example, serum and cells from a Group A person for the dilution of, and testing of, the serum suspected of containing hyperimmune anti-A), by successive dilutions with compatible human serum and the use of a 2 to 4 per cent suspension of known cells in serum. The hyperimmune A and B antibodies are inactive in saline solution and usually also in bovine as well as human albumin. Wiener⁴⁶ has found a buffered solution of acacia useful as a suspension medium. Group A₁ red cells should be used in the titration of a suspected hyperimmune anti-A, since the titer may be much lower against Group A₂ cells, or even absent, after the addition of the soluble antigen.

Trypsin as an Aid in Agglutination Techniques

The use of trypsin in blood-grouping techniques has been reported by Morton and Pickles⁴⁷ and studied extensively by others.^{48, 49} Exposure of normal red cells to a dilute solution of trypsin alters them so that they are immediately agglutinated by hyperimmune (or blocking) antibodies when suspended in saline solution. The use of trypsin or other appropriate enzymes to treat red cells promises to aid blood-grouping procedures by great simplification. The exact techniques have not had wide enough trial to be recommended for routine use.

SUMMARY

Seven blood-group systems are described comprising at least 20 separate and specific blood-group antigens. All are of very great importance in the fields of genetics, anthropology and legal medicine. At least 10 have been found responsible for cases of erythroblastosis fetalis. These same 10 have been found responsible for hemolytic transfusion reactions.

Although there is much confusion regarding the blood groups they are simple enough to understand when considered one by one, which is usually possible in clinical practice. The chief difficulty consists of considerable variability in the types of circulating antibodies, which may occur naturally or may be produced by active immunization against any one of the blood-group antigens. This variability makes necessary, in the present imperfect

state of technical procedures, a considerable battery of different testing methods. The principles, and essential technical details, of the important methods now in use are discussed.

Information essential to the understanding of what is presently known about the blood groups and their isoantibodies is included. The problems of erythroblastosis fetalis and hemolytic transfusion reactions are relatively clear cut so far as the A, B and D (Rh₀) antigens are concerned. Clinical problems caused by other antigens and antibodies are usually easily solved by any one of a number of laboratories specializing in this work.

Even though they seem complicated, the blood groups are of such practical importance that every practicing physician who is responsible for transfusions, who deals with obstetric problems or who cares for newborn babies should have a fair knowledge of the basic concepts of blood-group incompatibility, in order that he may avoid serious risks to his patients, and be prepared to treat promptly the results of antigen-antibody reactions involving the blood-group factors.

In the process of preparation of this material for the *Syllabus of Laboratory Examinations in Clinical Diagnosis*, the manuscript was edited, criticized, changed and otherwise manipulated by a large number of persons, in particular, Dr T Hale Ham, who is largely responsible for its having been undertaken at all. Dr R R Race, of London, kindly reviewed the manuscript in its final stages.

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MASSACHUSETTS MEDICAL SOCIETY

PROCEEDINGS OF THE COUNCIL

Stated Meeting, October 5, 1949

A STATED meeting of the Council was called to order by the President, Dr Arthur W Allen, on Wednesday, October 5, 1949, at 10 30 a m in John Ware Hall, Boston Medical Library, 8 Fenway, Boston

Two hundred and forty-one councilors were present (Appendix No 1)

The Secretary, Dr H Quimby Gallupe, presented the minutes of the Council meeting of May 23, 1949, as printed in the *New England Journal of Medicine*, issue of July 21, 1949 and moved their acceptance The motion was seconded, and it was so voted

The President then read the following obituaries

HAROLD GERARD GIDDINGS — Dr Harold Gerard Giddings died at his home on May 28, 1949 He was born in Gardiner, Maine, on March 23, 1880 He graduated from Harvard College in 1901 and from Harvard Medical School in 1907 After a surgical internship at the Massachusetts General Hospital, he took up general surgical practice in and around Boston Dr Giddings was chief of surgery at the Whidden Memorial Hospital in Everett from 1936 to 1947 and chief of the surgical outpatient department at the Massachusetts General Hospital from 1943 to 1946 During summer months he practiced surgery in Falmouth, Massachusetts In World War I, he served as a lieutenant colonel in the National Guard and commanded a Massachusetts Relief Expedition at the time of the Halifax explosion In World War II, he was a selective-service-board physician He was always actively interested in the affairs of the Society, serving on the procurement and assignment committee of Middlesex South District Medical Society and as president from 1943 to 1945 At the time of his death he had just finished his term as chairman of the Committee on Arrangements It was fortunate that he was able to attend the annual meeting of the Society in Worcester and to observe the appreciation of the fine program for which he devoted so much time and effort

He was a fellow of the American College of Surgeons

Dr Giddings loved his native state, he was an ardent fisherman and enjoyed his visits to Maine as a delegate to the Maine State Medical Society

HENRY ASHTON ROBINSON — Dr Henry Ashton Robinson died suddenly at his home in Hingham on August 21, 1949, in his sixty-third year

He was born in Hingham in 1887, attended the Hingham public schools and graduated from Harvard College in 1908 and Harvard Medical School in 1911

After practicing for several years in Marlboro, he was commissioned a first lieutenant in the United States Army in World War I and served in France with the 303rd Sanitary train of the 78th Division and was discharged as captain at the close of the war

In 1919 he settled in Hingham for the practice of medicine and was there until his death He was school physician for twenty-seven years and held other positions in social and business affairs of his town

He became a member of the Massachusetts Medical Society in 1914 and of the Norfolk South District Medical Society in 1919 He was a member of the Council from his district from 1938 to 1941 and from 1946 to 1949 He was vice-president of the Norfolk South District Medical Society in 1943 and president in 1944 and 1945 He was a member of the Committee on Public Relations from 1946 to 1949

In 1946 he was appointed to the Norfolk South District Committee to co-operate with the boards of public welfare and in 1947 was appointed chairman of the Norfolk South District Committee on School Medical Services

In January, 1948, he was appointed chairman of the Norfolk South District Committee of Professional Service Committee (Blue Shield) He was chairman of the Committee to organize a woman's auxiliary in this district

In 1949 he was appointed by Dr Belding a member of the Norfolk South District Legislative Committee He was a delegate two years ago to the meeting of the American Physicians Committee, after which he was active in planning a program for the Massachusetts Medical Society

His death leaves a vacancy in our ranks and we all realize that we have lost a tireless worker for the best interests of the Society

At the request of the President, the Council stood in silent tribute to the departed fellows

The President then announced the following interim appointments, which were approved by the Council

Committee on Code for Physicians

Donald Munro, *Chairman*
Charles C Lund
John F Conlin
Leroy A Schall
Ralph R Stratton

Committee on Pilot Clinics

John J Poutas, *Chairman*
Brooks Ryder
Sidney Cobb
George Dunlop
Alfred L Frechette

In addition to the following representatives from the districts

Julius G Kelley
George S Reynolds
William M Stobbs
Aubrey J Pothier
Elmer S Bagnall
Albert E Parkhurst
Spencer Flo
Allen S Johnson
Edward J Manwell
Robert E Archibald
Samuel A Dibbins
John J Poutas
Alfred L Frechette
Henry F Howe
Donald Martin
Brooks Ryder
George Dunlop
Sidney Cobb

President Allen then made the following remarks

The Committee to study the problem of professional service fees in the State was ordered by the Council at its last meeting to consist of 18 members — that is, one theoretically from each district In going over this problem, it seemed that it might serve a better interest for the Society if, in addition to these 18 men representing the various districts, we had a central executive committee representing the various specialties in medicine I will

state of technical procedures, a considerable battery of different testing methods. The principles, and essential technical details, of the important methods now in use are discussed.

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In the process of preparation of this material for the *Syllabus of Laboratory Examinations in Clinical Diagnosis*, the manuscript was edited, criticized, changed and otherwise manipulated by a large number of persons, in particular, Dr. T. Hale Ham, who is largely responsible for its having been undertaken at all. Dr. R. R. Race, of London, kindly reviewed the manuscript in its final stages.

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This recommendation was discussed in the Executive Committee, and apparently approved in principle, but not voted upon. It was suggested by the Executive Committee that the following recommendation replace that of the Committee on Public Relations:

That the Council shall establish a Massachusetts Medical Society citation to be awarded to a layman or a group of laymen for outstanding contributions to medical progress. Not more than three awards shall be made in any one year. The recipients shall be selected by a Committee to be designated by the President.

Also, the Executive Committee recommended that that citation should bear a name, and that the name should be the Lemuel Shattuck Award. I move you the adoption of the recommendation as presented by the Executive Committee.

The motion was seconded

Dr. Barton, Norfolk, spoke as follows:

The following remarks concern the naming of the award only. The presentation of the award as planned is an effort to improve relations between the Massachusetts Medical Society and the public, and in that respect it differs from some functions within the Society that bear the name of individuals, like the Cotting Luncheon.

If this citation is called by the name of an individual, it will gradually be referred to in the newspapers and elsewhere only by that name, and the Society's interest in it will be forgotten. Norfolk District Medical Society feels that when from time to time this award is made, it will emphasize the Massachusetts Medical Society's part in seeking out the recipient if the award is made in the Society's name.

We therefore recommend that the layman's award or citation bear the name "The Massachusetts Medical Society Citation for Outstanding Contributions to Medical Progress." I move the adoption of this recommendation.

This amendment was seconded.

Dr. John Fallon, Worcester, said that the Executive Committee believed that more publicity would be obtained by placing the name of Lemuel Shattuck on the citation. Mr. Shattuck was a layman who had produced one of the most important public-health documents.

The President called for a show of hands on Dr. Barton's amendment and declared that it was so voted. He then called for a voice vote on the main motion as amended and declared it so voted.

Dr. Kurth then moved the approval of the whole report as amended. The motion was seconded, and it was so voted.

Committee on Tax-Supported Medical Care — Dr. Albert A. Hornor, Suffolk, *Chairman*

Dr. Hornor submitted the report (Appendix No. 4) as informational and moved its acceptance. The motion was seconded, and it was so voted.

Committee on Legislation — Dr. David L. Belding, Norfolk South, *Co-Chairman*

Dr. Solomon L. Skvirsky, Norfolk, presented the report (Appendix No. 5) as informational and moved its acceptance. The motion was seconded, and it was so voted.

Subcommittee on National Legislation — Dr. Charles G. Hayden, Middlesex South, *Chairman*

Dr. Hayden presented the report as printed (Appendix No. 6) and mentioned the typographical error that had been corrected by the Executive Committee. He moved the acceptance of the informational report as corrected. The motion was seconded and it was so voted. Dr. Hayden said Reorganization Plan No. 1 mentioned in the report, had been defeated in the Senate.

STANDING COMMITTEES

Committee on Arrangements — Dr. Franklin G. Balch, Jr., Suffolk, *Chairman*

The Secretary presented the report for Dr. Balch (Appendix No. 7) and moved its acceptance with the recommendation concerning the time and place for the 1950 annual meeting. The motion was seconded, and it was so voted.

Committee on Public Health — Dr. Roy J. Ward, Worcester, *Chairman*

Dr. Ward presented the report (Appendix No. 8) as printed with two additions: telephone approval from his committee of the survey of multiple sclerosis by the Harvard School of Public Health and of the chest x-ray program in Boston. Dr. Ward made a motion that the Council also approve these two projects. The motion was seconded, and it was so voted. Dr. Ward then made a motion that certain very simple "standing orders" for nursing homes issued by the Department of Health approved by his committee be approved by the Council. The motion was seconded, and it was so voted.

Dr. Ward made a motion that the arthritic survey be approved and that it be accomplished with and through the office of the Commissioner of Health. The motion was seconded and so voted.

Dr. Ward made a motion that a sub-committee of his committee be appointed to study the problem of arthritis. The motion was seconded, and it was so voted.

He then moved for approval of the report as a whole. The motion was seconded, and it was so voted.

Committee on Membership — Dr. Lewis S. Pilcher, Middlesex South, *Chairman*

Dr. Pilcher presented his report as printed (Appendix No. 9) and spoke as follows:

The reason for discussing this report in some detail and giving special consideration to it is that the principal recommendation of the Committee on Membership concerns a problem that has been discussed before by the Council on several occasions, under differing conditions, and has been turned down. So we feel very strongly that this recommendation should be approved.

The recommendation concerns changing the by-laws as relates to application for membership of graduates of unapproved and foreign medical schools. Now, when

have to ask the Council to approve of this action on the part of the President, to make this change in the ruling, and the executive committee that we recommend is as follows

Richard H. Sweet, *Chairman*
George Prather
Leroy Schall
William Beetham
Christopher Duncan
Theodore Badger
Samuel Robins
Leo V. Hand
Richard I. Smith
Donald Munro
William T. Green

As representing the various districts, it seemed that the already appointed chairmen of Blue Shield district professional service committees would be best able to represent the Society as a whole. I will not read their names, unless you choose, but they have been previously appointed as such.

The two vacancies on the Council were filled as follows

Dr. Daniel B. Reardon — to replace Dr. Henry A. Robinson as public-relations councilor from Norfolk South

Dr. Joseph A. Holmes — to replace Dr. Harold G. Giddings on the Council from Middlesex South

REPORTS OF COMMITTEES

Executive Committee — Dr. H. Quimby Gallupe, Middlesex South, *Secretary*

The Secretary submitted the report of the Committee (Appendix No. 2), which met on September 7, 1949, at the Hotel Kenmore.

Under new business of the committee, the Secretary moved that the Council recommend to the Committee on By-laws and Council Rules that the by-laws be so changed that there shall be no fewer than six councilors elected from each district. The motion was seconded, and it was so voted without discussion.

The Secretary then moved that the President be asked to appoint a committee of 18 representing the district societies to study the problem of re-districting and councilor representation and, further, that an executive committee of not more than 7 members of the committee be appointed with power to act for the committee. The motion was seconded.

Dr. Basil E. Barton, Norfolk, moved that the motion be amended by changing the words "have power to act for the committee" to "for this purpose."

The motion to amend was seconded, and it was so voted. The President then called for a voice vote on the main motion, and it was carried unanimously.

Dr. Allen then spoke as follows:

May I now present to the Councilors a committee that we suggest to do this study concerning re-districting, and the number of councilors? It seemed to Dr. Gallupe and to me and to some others with whom we discussed this problem, that perhaps the secretaries of the various district societies would be the logical people to serve as a committee of 18 to study this problem. So we recommend the appointment of the secretaries of the various district societies.

I shall not read them all unless you request it, but I will read the committee of 7 who were selected as the executive committee, being those we considered centrally enough located to handle the problem from the standpoint of the metropolitan area, and they are as follows:

Dr. Charles G. Shedd, *Chairman*
Dr. Alexander A. Levi
Dr. Basil E. Barton
Dr. Donald Hight
Dr. Milton M. Sisson
Dr. Harold R. Kurth
Dr. Roy W. Layton

Dr. Ralph Stratton, Middlesex East, stated that Dr. Roy Layton had resigned as secretary of Middlesex East District Medical Society and that his successor had not yet come to function. Dr. Allen said that correction would be made.

A motion was made to approve the appointments, and it was seconded and so voted.

The Secretary then moved that the American Medical Association be invited to hold its Interim Clinical Session in Boston after 1950. The motion was seconded, and it was so voted.

The Secretary proposed that the choice of the Executive Committee for the American Medical Association's General Practitioner Award for 1949 had been made and that President Allen might well tell the Council about their candidate. Dr. Allen spoke as follows:

I feel that we are particularly fortunate in this state in having so many men who could qualify in this capacity. I believe that the Executive Committee gave very careful consideration to the three suggestions that were brought forth by three separate districts and it was felt that any one of these men would certainly have done credit to Massachusetts.

The vote, however, fell to one who is so well known to every man and woman who is a member of the Massachusetts Medical Society that I believe we should feel greatly honored to have him represent us. It is my hope that the entire Society in every conceivable way will back this candidate to the fullest of our abilities. We want him to win. We want him to bring this honor back to Massachusetts.

I will ask this candidate to rise, so that you will know personally he is still here and alive, and it looks as though we might win — Dr. Elmer S. Bagnall.

Committee on Public Relations — Dr. Harold R. Kurth, Essex North, *Secretary*

Dr. Kurth submitted the report as printed (Appendix No. 3). He then moved the approval of the first recommendation, that there be held a medical-press-radio conference some time in the latter part of October, 1949. The motion was seconded, and it was so voted.

Dr. Kurth then moved that the proposed health exhibit, which was to have been held in the fall of this year, be indefinitely postponed. The motion was seconded, and it was so voted. Dr. Kurth then spoke as follows:

The third recommendation was that the Council empower the Committee on Public Relations to award to some layman or group of laymen a citation for outstanding service to the medical profession, and that secondly, the Committee on Public Relations shall not make more than three such citations annually.

This recommendation was discussed in the Executive Committee, and apparently approved in principle, but not voted upon. It was suggested by the Executive Committee that the following recommendation replace that of the Committee on Public Relations:

That the Council shall establish a Massachusetts Medical Society citation to be awarded to a layman or a group of laymen for outstanding contributions to medical progress. Not more than three awards shall be made in any one year. The recipients shall be selected by a Committee to be designated by the President.

Also, the Executive Committee recommended that that citation should bear a name, and that the name should be the Lemuel Shattuck Award. I move you the adoption of the recommendation as presented by the Executive Committee.

The motion was seconded.

Dr Barton, Norfolk, spoke as follows:

The following remarks concern the naming of the award only. The presentation of the award as planned is an effort to improve relations between the Massachusetts Medical Society and the public, and in that respect it differs from some functions within the Society that bear the name of individuals, like the Cotting Lunchon.

If this citation is called by the name of an individual, it will gradually be referred to in the newspapers and elsewhere only by that name, and the Society's interest in it will be forgotten. Norfolk District Medical Society feels that when from time to time this award is made, it will emphasize the Massachusetts Medical Society's part in seeking out the recipient if the award is made in the Society's name.

We therefore recommend that the layman's award or citation bear the name "The Massachusetts Medical Society Citation for Outstanding Contributions to Medical Progress." I move the adoption of this recommendation.

This amendment was seconded.

Dr John Fallon, Worcester, said that the Executive Committee believed that more publicity would be obtained by placing the name of Lemuel Shattuck on the citation. Mr Shattuck was a layman who had produced one of the most important public-health documents.

The President called for a show of hands on Dr Barton's amendment and declared that it was so voted. He then called for a voice vote on the main motion as amended and declared it so voted.

Dr Kurth then moved the approval of the whole report as amended. The motion was seconded, and it was so voted.

Committee on Tax-Supported Medical Care — Dr Albert A. Hornor, Suffolk, *Chairman*

Dr Hornor submitted the report (Appendix No 4) as informational and moved its acceptance. The motion was seconded, and it was so voted.

Committee on Legislation — Dr David L. Belding, Norfolk South, *Co-Chairman*

Dr Solomon L. Skvirsky, Norfolk, presented the report (Appendix No 5) as informational and moved its acceptance. The motion was seconded, and it was so voted.

Subcommittee on National Legislation — Dr Charles G. Hayden, Middlesex South, *Chairman*

Dr Hayden presented the report as printed (Appendix No 6) and mentioned the typographical error that had been corrected by the Executive Committee. He moved the acceptance of the informational report as corrected. The motion was seconded and it was so voted. Dr Hayden said Reorganization Plan No 1, mentioned in the report, had been defeated in the Senate.

STANDING COMMITTEES

Committee on Arrangements — Dr Franklin G. Balch Jr, Suffolk, *Chairman*

The Secretary presented the report for Dr Balch (Appendix No 7) and moved its acceptance with the recommendation concerning the time and place for the 1950 annual meeting. The motion was seconded, and it was so voted.

Committee on Public Health — Dr Roy J. Ward, Worcester, *Chairman*

Dr Ward presented the report (Appendix No 8) as printed with two additions: telephone approval from his committee of the survey of multiple sclerosis by the Harvard School of Public Health and of the chest x-ray program in Boston. Dr Ward made a motion that the Council also approve these two projects. The motion was seconded, and it was so voted. Dr Ward then made a motion that certain very simple "standing orders" for nursing homes issued by the Department of Health approved by his committee be approved by the Council. The motion was seconded, and it was so voted.

Dr Ward made a motion that the arthritic survey be approved and that it be accomplished with and through the office of the Commissioner of Health. The motion was seconded and so voted.

Dr Ward made a motion that a sub-committee of his committee be appointed to study the problem of arthritis. The motion was seconded, and it was so voted.

He then moved for approval of the report as a whole. The motion was seconded, and it was so voted.

Committee on Membership — Dr Lewis S. Pilcher, Middlesex South, *Chairman*

Dr Pilcher presented his report as printed (Appendix No 9) and spoke as follows:

The reason for discussing this report in some detail and giving special consideration to it is that the principal recommendation of the Committee on Membership concerns a problem that has been discussed before by the Council on several occasions, under differing conditions, and has been turned down. So we feel very strongly that this recommendation should be approved.

The recommendation concerns changing the by-laws as relates to application for membership of graduates of unapproved and foreign medical schools. Now, when

this by-law was originally written, there was an influx of refugee physicians to the United States, particularly to Massachusetts. There were several unapproved medical schools within Massachusetts that were turning out large numbers of graduates each year, and it was felt that the Society had to protect itself by passing this by-law, which refused these graduates the right to apply for membership until they had been licensed for five years.

I want to call attention to the fact, however, that this by-law did not say that they had to be licensed in Massachusetts, or that they had to be residents of Massachusetts. They could come to Massachusetts after having been licensed anywhere in the United States, and as far as the by-laws are concerned, they could be in Massachusetts just one day before applying for membership in the Massachusetts Medical Society. The members of our Committee felt that that by-law, as far as the five-year provision was concerned, was no longer necessary, for the chief reason that refugee physicians are no longer a problem in this state, and secondly, that as of this year, all the unapproved medical schools in the country have been closed.

The objections to changing the by-laws are that if we do not have such a long waiting period, the physicians in the community will not have as long an opportunity to become acquainted with these applicants, and, of course, it is upon the other physicians in the community that we consider admitting these applicants to the Society.

However, under the old by-laws they did not have to be residents of the community. There was no residence requirement, and I should like to point out that under the by-laws of the Society it is the job of the Committee on Membership to satisfy itself that an applicant to membership is suited for membership, and any applicant who applies for membership in the Society who comes from an unapproved school, or who has any questionable background, is very thoroughly investigated by the Committee. We do not accept the letters that come with the application, which, everybody recognizes, may be written under pressure or may be just a formality. We call up in the community. We call up the members of the district committee and ask them to come in and discuss these men, and if there is still any question in our minds, we postpone the application for six months for further investigation. Thus, there are adequate safeguards within the Committee on Membership to assure that anybody who applies for membership in the Society will not be admitted if he should not be. And it does not require protection in the by-laws.

I should therefore like to move approval of the recommendation of the Committee on Membership to change the by-laws, Chapter V, Section 2 (b), second paragraph, to read as follows: "The applicant has possessed a license to practice medicine in the Commonwealth and has conducted that practice in the district in which he makes application for at least one year."

The motion was seconded.

Dr Frank R. Ober, Suffolk, spoke against the motion. Dr Philip G. Berman, Middlesex North, made a motion to amend, substituting two years for one year. The motion was seconded and defeated on a voice vote.

Dr Charles C. Lund, Suffolk, Dr H. Quimby Gallupe, Middlesex South, Dr Carl Bearse, Norfolk, and Dr Peirce H. Leavitt, Plymouth, spoke in favor of the main motion.

The President put the motion, and it was carried. Dr Pilcher moved that the report as a whole be approved. The motion was seconded, and it was so voted.

Committee on Society Headquarters — Dr Frank Ober, Suffolk, Chairman

Dr Ober presented his report as printed (Appendix No. 10) and spoke as follows:

We all recognize that in the last eight or nine years since Dr Phippen was president, the things that he instituted have outgrown the Society's headquarters. And the question is whether we should go into the matter of headquarters, doing something to revamp this building, or whether we should combine with some other institution or go out and select a piece of land of our own. We have had an opportunity to combine with the Museum of Natural History on the site of land down near the Charles River Dam. There are only 6 acres there.

The School of Public Health at Harvard University is going to move away from its present headquarters, if they can build a building. They are anxious to have the Department of Health in the same location, because their functions are more or less interwoven, and many men do teaching from the Department of Public Health and many in the School of Public Health give advice to the Department.

Then, too, we must consider the Library and the *Journal*, and the Society, which would be under the same roof, or under closely neighboring roofs.

There are great advantages in being connected with the Department of Public Health and the School of Public Health at Harvard, if we could have a site of land, which I am quite sure we could obtain for a small sum, not far away, where there is sufficient parking space (about 14 acres). It would hinge on selling this.

Now, if we add to the present building by constructing a piece across the corridor in the area at the back, we have something that will last temporarily, but we should decide whether we shall be satisfied with something temporary, or do we want something that will last indefinitely? As we discussed this matter, one of the members of the Committee suggested that instead of having the doctors study this situation, it would be much better if we could get a man who was competent in the field to study all the plans, and make recommendations to the committee, which we can present to the Council.

Dr Ober moved that the study be made. The motion was seconded, and it was so voted. Dr Ober then moved that a sum not exceeding \$5000 be appropriated to cover the cost of such a study. The motion was seconded, and it was so voted. Dr Ober then made a motion to approve the report as a whole. The motion was seconded, and it was so voted without discussion.

Committee on Industrial Health — Dr Henry C. Marble, Suffolk, Chairman

The Secretary presented the report as printed (Appendix No. 11) for the chairman. He noted that the date for the Industrial Health Conference had been changed to December 14, 1949. The Secretary moved the approval of the report as a whole with its recommendation. The motion was seconded and it was so voted.

SPECIAL COMMITTEES

Committee to Meet with the Massachusetts Hospital Association — Dr Albert E. Parkhurst, Essex South, Chairman

Dr Harvey Morrison presented the report (Appendix No. 12) as informational and moved its acceptance. The motion was seconded, and it was so voted.

Dr Albert Hornor made a motion that the Council extend its thanks to the Committee and request it to report further progress at the next meeting of

the Council The motion was seconded Dr McKittrick made the following remarks

I hope this isn't entirely out of order, but I should like to put my nickel's worth in Now, this committee cannot do this job I am not a member of the committee but I have put a lot of time and effort on this problem and any committee appointed isn't going to be able to do this job This job is going to be done at a local level, and that local level represents the individual hospitals We have been going through this at the Massachusetts General Hospital We have been bogged down not by the problem that is under discussion but by certain other matters that complicate it And we have eventually agreed almost in total with this report It has been done in certain other hospitals in the State and it has been done in hospitals outside this state

I should like to suggest that the Committee not be burdened with too much responsibility but that every one start working at the local level, and get the ball rolling for conferences between administration and between staffs

The so-called McKittrick report can be taken as the basis from which discussion starts and if individual hospitals will do that, continuous pressure will not be put on this committee, which can only go so far and no farther

The Secretary made the following statement

I want to second what Dr McKittrick has said, and to refer you all to the proceedings of the House of Delegates of the Annual Meeting of the American Medical Association held in Atlantic City last June, because there you will find the Hess Committee report, which every one of you should read, because it probably will mean the solution of your troubles, if you have any with your local hospital And that committee report includes in it the McKittrick report, the Report on Special Services, which, I wish to tell you, is a monument to the efforts of that committee and the Society in this whole problem

The President put the main motion, and it was so voted

Committee on Postgraduate Medical Education — Dr W Richard Ohler, Norfolk, Chairman

The Secretary presented the report as printed (Appendix No 13) for Dr Ohler as informational and moved its acceptance The motion was seconded, and it was so voted

Committee on Medical Economics — Dr Elmer S Bagnall, Essex North, Chairman

Dr Bagnall submitted the report as printed (Appendix No 14) and moved the approval of the new wording of Principle No 13 The motion was seconded

Dr Hornor opposed the motion for reasons that he mentioned as follows

I don't think it is going to do us any good to put such a thing in It is none of our business whether the schools go out for assistance or not.

Before the Congress at present is a bill embodying this idea, in which it has been insisted that funds must be furnished for schools for the education of osteopaths

I believe that schools that are now unworthy, which just hold charters and are not really operating, can use this to go to the federal Government and get money and we shall see an increase in unworthy schools

Dr Vlado A Getting, Middlesex South, spoke as follows

Being the administrator of a department that is now receiving between \$2,000,000 and \$3,000,000 in federal

funds today, I should perhaps tell you the experience we have had regarding any attempted control from the federal Government over a state program There isn't any If the Great White Father in Washington puts out regulations and rules that seem to be stringent, all we have to do is make a complaint, and the rules are changed immediately

I will say frankly that throughout the country, as a whole, the quality of public-health practice is greatly increased as a result of federal grants-in-aid for research and that every dean that the American Academy of Pediatrics representatives have communicated with has indicated not only that he is willing to accept the money but also that his experience has been good

As a member of the Approving Authority for Medical Schools it was our responsibility, and Dr Gallupe can well vouch for this, to look into the finances of training medical students The costs have gone up tremendously The income of the schools has not kept pace with the expenses

I believe that it is in the interests of the training of physicians to make it possible for them to receive money from the Government, if the Government wants to give it to them

In the Committee on Medical Economics and in the Committee on National Legislation of which committees I happen to be a member, it was decided that we in our letters to Congress would indicate that the Society is not in favor of any legislation that would support schools of osteopathy, so that complaint would be taken care of I think on the whole that this point No 13 as now written will be of benefit to all three medical schools in Massachusetts I think that if even the president of Princeton, who said he would not accept federal funds, carefully analyzed his budget, he would find that a great deal of funds now used for research in Princeton are from a federal source

Dr Charles G Hayden made the following statement

As a matter of information, I should like to point out that the bill now before Congress, which would provide for the subsidization of medical schools, was drawn in cooperation with the American Medical Association For that reason, I feel that it rightly comes within the province of this group to take action one way or another on this matter

Secondly, along the line of Dr Getting's remarks, as chairman of the Subcommittee on National Legislation, I have already sent a protest regarding the provision for subsidies for schools of osteopathy

The President put the question, and Dr Bagnall's motion was passed Dr Bagnall then made a motion to approve the report as a whole The motion was seconded, and it was so voted

Committee on New England Postgraduate Assembly — Dr Richard P Stetson, Suffolk, Chairman

The Secretary presented the informational report as printed (Appendix No 15) for the chairman and moved its acceptance The motion was seconded, and it was so voted

Committee on Diabetes — Dr Howard F Root, Suffolk, Chairman

Dr James H Townsend, Middlesex South, presented the report as informational (Appendix No 16) and moved its acceptance The motion was seconded, and it was so voted

The Co-ordinating Committee — Dr Frank H Lahey, Suffolk, *Chairman*

The Secretary presented the informational report (Appendix No 17) and moved its acceptance. The motion was seconded, and it was so voted.

Committee on Publicity Code — Dr Donald Munro, Suffolk, *Chairman*

Dr Munro presented the report as printed (Appendix No 18) and moved acceptance of the code as written in the report. The motion was seconded.

Dr Barton and Dr Norman A Welch, Norfolk, objected to Section 6 of the code because the words "head of a major department or research organization" might refer to the head of a commercial organization who might not be a physician. Dr Barton moved to amend the report by further study of Section 6. The motion was seconded.

Dr Munro said the code applied only to fellows of the Society and stated that Section 2 was the governing paragraph as to who would come under the code.

Dr McKittrick suggested that a comma placed after "hospitals" in line 1 of paragraph 6 would be helpful. On a show of hands Dr Barton's amendment was defeated. On a voice vote, Dr Munro's motion passed.

Dr Munro then moved the adoption of the second recommendation to continue the committee. The motion was seconded, and it was so voted.

Dr Munro moved the adoption of the third recommendation to publish the code in the new pamphlet on by-laws. The motion was seconded, and it was so voted. Dr Munro made a motion to accept the report as a whole. The motion was seconded, and it was so voted.

Report of Meeting of House of Delegates of the American Medical Association

Dr Leland S McKittrick, Suffolk, presented the report as printed (Appendix No 19) and moved its acceptance. The motion was seconded, and it was so voted.

Dr John Fallon, Worcester, spoke as follows:

At the last meeting of the House of Delegates, they asked that district and state societies institute committees to deal with hospital relations. Our committee under the name of the Committee to Meet with the Massachusetts Hospital Association has been doing that for a long time, and simply to get the thing in line with the American Medical Association terminology, I move that the name of this committee — and the Executive Committee approved the change — be changed to the Committee on Hospital and Professional Relations.

The motion was seconded, and it was so voted.

Advisory Committee on Red Cross Blood Bank — Dr Lamar Soutter, Suffolk, *Chairman*

Dr Carl Bearse, Norfolk, said that since neither the chairman nor any other member of the com-

mittee was present, he moved that the report be deferred. The motion was seconded.

Drs McKittrick, Gallupe, Lund and Parkins spoke against this motion because of the importance of the report. Dr Getting spoke as follows:

The Department of Public Health appropriates about \$150,000 as joint sponsor of this program. The Red Cross is spending in round figures about half a million dollars for the blood program, for the collection of the blood and for processing. In addition to that, they have in Massachusetts a pilot plant in our laboratory, where new procedures and techniques are developed after they are first tested in Dr McCoombs's laboratory at Harvard Medical School.

I believe that the purpose of this report is to improve the public relations between the hospitals, the profession at large and the American Red Cross and it is particularly important right now for the simple reason that this fall the American Red Cross will be opening a permanent blood center here in Boston, and while I can well understand the reluctance of the Council to act upon this matter, in the absence of a member of the committee, I believe that it is an oversight and I believe that the merits of the report speak for themselves.

The Secretary moved the adoption of the whole report as printed (Appendix No 20). The motion was seconded, and it was so voted.

Subcommittee of the Executive Committee on Blue Cross-Blue Shield Problems — Dr Charles J E Kickham, Norfolk, *Chairman*

Dr Kickham presented the report as amended by the Executive Committee (Appendix No 21). Concerning the only recommendation of the committee, Dr Kickham spoke as follows:

As we know, some physicians on an office basis have become members of Blue Shield, but up to the present time we understand that the association of groups of doctors or groups of physicians getting on the hospital basis, as in the Blue Cross, has not been carried out, and it was the opinion of the Committee that this discussion should be referred to an appropriate committee and brought back at a coming meeting of the Council. The Executive Committee voted that this present committee be empowered to investigate this subject more fully and to report to the Council. I, therefore, move the acceptance of the report in addition to the recommendation of the Executive Committee.

Dr Charles Hayden made the following remarks:

Again as a matter of information I should like to call attention to the fact that we receive upwards of half a dozen requests each week from physicians who want to join Blue Shield. Prior to September 1 of this year, we had no nongroup program and because physicians by and large are not associated with eligible groups, we were able to turn down those requests, giving them the information that the matter had been discussed by the Committee on Public Relations previously and that it was the policy of the Society not to make any arrangements for Blue Shield enrollments as have been made for Blue Cross enrollment. Now, under our present nongroup contract, I see no legal way in which we can turn down any physician who applies, provided he meets the qualifications that have been established for nongroup enrollment.

Dr James C McCann, Worcester, then spoke as follows:

In New York State the prepayment group had given little consideration to disruption of teaching services, since they are formally organized with the arrangement of limited staff members to teach the students associated

with the schools and colleges coming to those hospitals. We knew from the New York groups that private patients and beds in the teaching corridors could be interspersed with the teaching beds and that the effort of the teaching group was seriously disrupted.

The Blue Shield group called a meeting requesting the men in the teaching hospitals to advise us how we might maintain the objectives of prepayment and still not disrupt the teaching efforts in the schools and teaching hospitals. The suggestion was that we adopt the policy that we have previously used in payment of men associated with private groups—that is, checks were sent to a designated member of the group and the disposition of funds was then determined by the practitioners in that group.

There are several private groups in the State and the policy of those groups is to assure that all their members are participating physicians, so that then one saves the immense inconvenience of determining who in a group operates on a private patient—the Blue Shield compensates that group as such for all work done under the auspices of that group.

The suggestion of the teaching group was that we simply send out patients to them as formally organized groups, with the assurance that they would so organize. I think that the question of what is the ultimate fate of those funds, once the monies are placed in the hands of those physicians, probably is their concern. Just what the ultimate decision of these several groups will be—whether they distribute the money among themselves or whether they will of their own volition use it for research purposes—they will determine, and offhand I do not feel that Blue Shield should further supervise the fate of those funds other than seeing that they are placed in the hands of the men who are responsible for the care of the patient.

Dr. Allen put the question and it was so voted.

Advisory Committee to the Woman's Auxiliary—Dr. John F. Conlin, Suffolk, *Chairman*.

The Secretary presented the report as printed (Appendix No. 22) and moved its acceptance. The motion was seconded, and it was so voted.

NEW BUSINESS

Dr. Lund, speaking for a committee appointed by the councilors of Suffolk District Medical Society, presented the following resolution:

Whereas a statement dealing with the treatment of diabetes quoting Dr. Michael Samokian, a biochemist, and released by the American Chemical Society has been printed prominently in the public press, and

Whereas this statement referring to the chronic insulin poisoning and stating that virtually all adult victims of diabetes can be restored to normal health and life comfortably, without insulin injections, leads to the interruption of established treatment, and consequently endangers the health and life of diabetics,

Be it resolved that the Council of the Massachusetts Medical Society recommends that any information pertaining to the diagnosis and treatment of disease be released to the public only with the approval of a responsible committee or authorized officer of the organization from which the release emanates, and

Be it further resolved that the delegates of the Massachusetts Medical Society to the American Medical Association be instructed to present this resolution to the House of Delegates of the American Medical Association and the request that the trustees recommend that this action be taken by all scientific organizations, and in addition, to offer the advisory services of the American Medical Association and its constituent societies to all such organizations.

Dr. Lund made a motion to suspend the council rules for the resolution to be discussed. The motion was seconded, and it was so voted unanimously.

Dr. Munro said he approved of the resolution but believed it should be rewritten to comply with the code adopted at this meeting. He made the following motion: "to amend this resolution by adding a further paragraph to it, to the effect that this resolution be referred for final form and structure to a committee of this society, which shall be designated by the President before publication in public print and other mediums." The motion was seconded.

Dr. Fallon said he believed the resolution should be clarified before presentation to the House of Delegates. He made the motion to table. The motion was seconded and it was so voted.

A motion to adjourn was made and seconded, and it was so voted at 1:05 p.m.

H. QUIMBY GALLUPE, M.D., *Secretary*

APPENDIX NO. 1

ATTENDANCE OF COUNCILORS

BARNSTABLE	HAMPDEN
D. E. Higgins	M. S. Allan
	E. P. Bagg
BERKSHIRE	R. L. Barrett
J. H. Fierman	Adolph Franz, Jr.
C. T. Leslie	J. M. Gilchrist
Helen M. Scoville	A. M. Glickman
P. J. Sullivan	Frederic Hagler
	D. R. Hayes
BRISTOL NORTH	S. F. Potsubay
J. H. Brewster	L. A. Putnam
C. N. Burden	A. G. Rice
M. E. Johnson	G. L. Schadt
J. L. Murphy	J. A. Seaman
W. M. Stobbs	H. N. Simpson
BRISTOL SOUTH	HAMPSHIRE
R. B. Butler	E. J. Manwell
D. F. Gallery	J. G. Pekala
R. H. Goodwin	
M. T. MacDonald	MIDDLESEX EAST
A. J. Pothier	J. L. Anderson
C. C. Tripp	T. P. Devlin
ESSEX NORTH	Robert Dutton
E. S. Bagnall	E. M. Halligan
W. J. Bain	K. L. MacLachlan
J. T. Batal	I. W. Richardson
Z. W. Colson	R. R. Stratton
J. F. Curtin	J. M. Wilcox
A. P. George	MIDDLESEX NORTH
H. R. Kurth	P. G. Berman
P. J. Look	W. M. Collins
R. C. Norris	S. A. Dibbins
F. W. Snow	L. J. Hall
F. N. Sweetsir	L. F. King
C. F. Warren	A. J. Stewart
C. A. Weiss	J. D. Sweeney
ESSEX SOUTH	H. A. Titus
Bernard Appel	MIDDLESEX SOUTH
W. W. Babson	E. W. Barron
L. F. Box	Harris Bass
Gerard Cote	J. M. Baty
T. J. Foote	L. A. Blacklow
S. N. Gardner	H. K. Bloom
M. H. Pett	G. F. H. Bowers
E. D. Reynolds	Madelaine R. Brown
H. D. Stebbins	R. N. Brown
C. F. Twomey	J. F. Casey
R. J. Williams	C. W. Clark
FRANKLIN	E. A. Cooney
L. R. Dame	W. H. Crosby
	H. J. Crumb

J A Daley
C L Derrick
J G Downing
A G Englebach
W C Feeley
C W Finnerty
J M Flynn
H Q Gallupe
V A Getting
H W Godfrey
A D Guthrie
C G Hadden
Eliot Hubbard, Jr
F R Jouett
L G Kendall
H A Kontoff
A A Levi
A N Makechmie
R A McCarty
Dudley Merrill
C E Mongan
Dwight O'Hara
Fabyan Packard
L S Pilcher
Max Ritvo
L G Rondeau
M J Schlesinger
E W Small
H P Stevens
A B Toppan
J H Townsend
J E Vance
C F Walcott
R H Wells
B M Wein

NORFOLK

C E Allard
B E Barton
Carl Bearse
Elizabeth Broyles
J H Caulcy
G L Doherty
Albert Ehrenfried
P S Foise
Susannah Friedman
D L Halbersleben
J A Halsted
R J Heffernan
L F Johnson
C J Kickham
C J E Kickham
D L Lionberger
D S Luce
C M Lydon
T F P Lyons
F P McCarthy
H L McCarthy
R T Monroe
H R Morrison
Hyman Morrison
D J Mullane
H A Novack
J J O'Connell
E E O'Neil
R S Palmer
G W Papen
S H Proger
H A Rice
D D Scannell
J A Seth
L A Sieracki
S L Skirsky
E S Smith
Kathleene S Snow
J W Spellman
A R Staggs
W J Walton
N A Welch
W A White, Jr
G F Wilkins
P R W
Marjory

NORFOLK SOUTH

D J Bailey
Harry Braverman
R L Cook
F W Crawford
Frederick Hinchcliffe
E K Jenkins
N R Pillsbury
D B Reardon

PLYMOUTH

J C Angley
H H Hamilton
P H Leavitt
D A Martin
C D McCann
Mildred L Ryan

SUFFOLK

H L Albright
M D Altschule
C H Bradford
W J Brickley
W E Browne
A M Butler
A J A Campbell
E M Chapman
M Henry Clifford
A P DerHagopian
Maurice Fremont-Smith
Joseph Garland
G L Gately
R L Goodale
A A Hornor
H A Kelly
H E Kennard
T H Lanman
R I Lee
C C Lund
C F Maraldi
L S McKittick
Donald Munro
H L Musgrave
F R Ober
J P O'Hare
L E Parkins
Helen S Pittman
J J Regan
W H Robey
C G Shedd
R M Smith
C M Stearns
Conrad Wesselhoeft

WORCESTER

A W Atwood
George Ballantyne
Jacob Brem
J B Butts
F B Carr
G R Dunlop
John Fallon
Thomas Hunter
H L Kirkendall
D G Ljungberg
J A Lundy
J C McCann
D K McClusky
J M Olson
F A O'Toole
E L Richmond
N S Scarcello
R J Ward
B C Wheeler
J J Tegelberg

WORCESTER NORTH

J J Curley
K J Jolma
G P Keaveny
J P Marnane
J V McHugh
J G Simmons

APPENDIX NO 2

REPORT OF THE EXECUTIVE COMMITTEE

After lunch at the Hotel Kenmore on September 7, 1949, the meeting of the Committee was called to order at 1:00 p. m. by Dr Arthur W Allen with all the officers of the Society, Dr John F Conlin, Dr Joseph Garland and sixteen of the eighteen councilors present.

Under new business before the committee, the Secretary presented the following:

Under the existing by-laws (Chapter III, Section 5) the ratio of councilors is 1 for every 20 fellows, and in the same section the by-laws demand the election in each district of at least 6 councilors to designated offices.

As a result, four of the district societies are not permitted to have the required number of councilors, and, therefore, some fellows have to fill two positions.

The Secretary pointed out that the present council is too large (365) for the present seating and luncheon facilities, that one first-class mail to councilors cost over \$100 and that in districts such as Middlesex South it is often difficult to find 59 fellows as councilors.

The Secretary suggested that the present difficulties might be solved by a change in the ratio to 1 councilor to 40 fellows and that no district shall have fewer than 6 councilors. If this were done, twelve districts would each have the necessary 6 councilors, two districts between 6 and 10, two districts between 10 and 20, and the remaining two between 30 and 40. Instead of 365, the council would number nearer 270.

Dr John Fallon, Worcester, stated that when the present by-laws were written this matter had been considered, but he thought that the matter should be placed in the hands of a committee to study redistricting. He agreed that the present council is too large, but believed that it increased the interest of a larger number of fellows in the affairs of the Society.

The Secretary said that the matter of redistricting was the second to be considered under new business, since it was apparent that a district such as Middlesex South was spread over too large an area and that fellows in Charlestown and Somerville found it difficult to be interested in Framingham's problems.

Dr Dame, Franklin, stated that he thought the matter of a minimum number of councilors was the most pressing at this time and moved that the Executive Committee recommend to the Committee on By-laws and Council Rules that there shall be no fewer than 6 councilors per district. The motion was seconded, and it was so voted.

Dr Fallon suggested that a committee be appointed to study redistricting and the ratio of councilors. Dr Hornor, Suffolk, suggested that the committee might be a small one appointed by the President, a representative from each district or a representative from the hospitals over the State as members, along the lines suggested by Dr Fitz several years ago.

Dr Hurlburt, Plymouth, said he thought that redistricting was mostly a metropolitan problem. Dr Mernam, Middlesex South, suggested that the new Advisory Board might study the problem. Dr Curley, Worcester North, said he thought the committee might best consist of 3 fellows from the Boston area and 4 others spread over the State.

Dr Fallon moved that it be recommended to the Council that the President appoint a committee of 18 representing each district to study the problem of redistricting and councilor representation, and further, that an executive committee of not more than 7 of the committee have power to act. The motion was seconded, and it was so voted.

The Secretary then gave the status of the American Medical Association assessment collection as follows:

At the end of July only 49 per cent of our membership had paid. A letter was written to those who had not paid and now the percentage is near 66. The Secretary paid and now the percentage is near 66. The Secretary has now turned over further collection to the districts, hoping that by close contact the percentage paying might rise to 80 or 85.

The Secretary said that the Boston Chamber of Commerce wishes the Society to invite the American Medical Association to hold the interim clinical session in Boston.

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after 1950 and assures the Society that exhibit and hotel space is available in sufficient quantity.

Dr Kickham Norfolkt moved that the Committee recommend that the Society invite the American Medical Association to hold the interim session in Boston at a future date. The motion was seconded and it was so voted.

The Secretary stated that the next item for consideration was the selection of the Massachusetts Medical Society candidate for the American Medical Association's General Practitioner's Award as directed by the Council. He said he knew of three candidates from Essex North Dr Elmer S Bagnall from Norfolk Dr Dean S Luce and from Worcester Dr William E. Balmer. These fellows had been officially chosen by their respective district societies.

At the request of the President Dr Arnold P. George Haverhill presented the name of Dr Elmer S Bagnall as the candidate from the Essex North District Medical Society and submitted a volume of material concerning Dr Bagnall. By a vote of the committee the material was passed around for inspection.

Dr Charles J. E. Kickham Norfolkt presented the name of Dr Dean S. Luce as the candidate of his district and submitted material concerning Dr Luce which was passed around.

Dr John Fallon Worcester presented the name of Dr William E. Balmer as the candidate of his district and submitted material concerning Dr Balmer.

Dr Allen asked Dr Conlin to say something about the public-relations aspect of the award. Dr Conlin spoke as follows:

I was just trying to go back to the original purpose in making this award. The requirements were never too clearly stipulated. It was to be a person who had been engaged in general practice exclusively, who was honored and respected within his community, and who had contributed to the well-being and respect for medicine in his community. At such time as a practitioner is selected for the award, by the vote of this Executive Committee it becomes a function of the public-relations branch of the Society to make something of it. That is the purpose of the award on a national basis and I think it should guide the choice of this committee. That is what can benefit medicine in Massachusetts from the choice of such a person.

Obviously, it is a public-relations gesture, purely and simply. That is why it was designed to get the people of American thinking about the function of the kindly, old family doctor, who had borne the burden through the years and was the backbone of the medical profession and all those other things that we have heard so much about. It means that the selection emerging from this group should be one that has some chance of emerging nationally.

The President then called for a vote by ballot and named Drs Welch and Garland as tellers. While the tellers collected the ballots and returned to count them, Dr Allen spoke as follows:

Whichever candidate should be selected by the Executive Committee, I think that we should support that candidate to the very best of our ability. Now there are three excellent men whose names have been submitted, and any one of them would do credit to the State. Now, of course, two of these men will have to be defeated unfortunately, but whichever man does get the most votes, or is selected, I hope that we will spread throughout the State in every district the word that this has been done as legally as we know how that this candidate has been selected and that we hope there will be a complete accord in the State and that everybody will support this candidate to the best of his ability because it would be quite an honor to bring this award to Massachusetts if it can possibly be done.

Dr Garland then announced that Dr Elmer S. Bagnall had been selected. Dr Kickham moved that the vote be made unanimous. This motion was seconded, and it was so voted.

At this point, Dr John Curley asked for support of the World Health Organization.

COMMITTEE REPORTS

Committee on Public Relations

Dr Allen presented the recommendation that a medical press-radio conference recommended by Dr Conlin be held during the latter part of October 1949. A motion was made to approve this recommendation. The motion was seconded and it was so voted without discussion.

Dr Allen presented the second recommendation that the Health Exhibit proposed for the fall of 1949 be indefinitely postponed because plans could not be completed in time. It was moved and seconded that the Council approve this recommendation. The motion was seconded and it was so voted without discussion.

Dr Allen then presented the third recommendation concerning lay awards. The Secretary moved that the Committee recommend that the Society make awards to laymen as described in the report. The motion was seconded. The Secretary reported that after communicating with all the other states on this matter, he found that a few had made lay awards and they all thought it a fine idea. Dr Dame said he believed the Society should produce a citation of merit which would be given to one who deserved it, rather than just pick out a person to honor. Dr Conlin spoke at length on the public-relations value of the award.

The original motion was withdrawn and the President asked Dr Dame to draw up a substitute motion embracing the points brought out in discussion—namely, the citation, the number of awards, the choice by the public-relations group, the need for careful publicity and the value of naming the citation.

While Dr Dame and Dr Conlin were conferring on the wording of a motion the President voted that the remainder of the report was informational. The Secretary moved the acceptance of the report as a whole, and it was so voted.

Dr Dame then made the following motion: "That the Council establish a Massachusetts Medical Society citation to be awarded to a layman or a group of laymen for outstanding contributions to medical progress. Not more than three awards shall be made in any one year. The recipients shall be selected by a committee to be designated by the President."

Dr Fallon suggested that the citation should bear a name, and Dr Garland said that probably Lemuel Shattuck had made the greatest contribution to Massachusetts. Dr McKittick said he thought the committee and the Council should be briefed on Lemuel Shattuck. (The discussion ended here without a second to Dr Dame's motion; however, the Committee was not antagonistic and were in favor of naming the citation.)

Information obtained by the Secretary revealed that under a resolve of the Legislature on Mar. 2, 1849, Mr Shattuck was named the chairman of a commission to produce a sanitary survey of the State. The report was published in 1850. Its proposal was the creation of state and local boards of health then nonexistent. The report was perhaps the most significant single document in the history of public health.

STANDING COMMITTEES

Committee on Tax-Supported Medical Care

This report was submitted by the President as informational. It was moved, seconded and voted to approve the report.

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The report was approved as informational.

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This report was approved as informational. At the request of the President, Dr Haven said that the letters were printed because of their interest and for the information of the Councilors, that Senator Lodge could not be convinced to vote our way and that Senator Smith of Maine could not be won over. Dr Allen commented on the excellent job done by the committee during the hot summer. Dr Hornor called attention to the fact that the year "1938" should be changed to "1948". The amended report was then approved by vote of the committee.

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C L Derrick
J G Downing
A G Englebach
W C Feeley
C W Finnerty
J M Flynn
H Q Gallupe
V A Getting
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A D Guthrie
C G Hayden
Eliot Hubbard, Jr
F R Jouett
L G Kendall
H A Kontoff
A A Levi
A N Makechnie
R A McCarty
Dudley Merrill
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Dwight O'Hara
Fabyan Packard
L S Pileher
Max Ritvo
L G Rondeau
M J Schlesinger
E W Small
H P Stevens
A B Toppan
J H Townsend
J E Vance
C F Walcott
R H Wells
B M Wein

NORFOLK

C E Allard
B E Barton
Carl Bearse
Elizabeth Broyles
J H Cauley
G L Doherty
Albert Ehrenfried
P S Foiese
Susannah Friedman
D L Halbersleben
J A Halsted
R J Heffernan
L F Johnson
C J Kickham
C J E Kickham
D L Lionberger
D S Luce
C M Lydon
T F P Lyons
F P McCarthy
H L McCarthy
R T Monroe
H R Morrison
Hyman Morrison
D J Mullane
H A Novack
J J O'Connell
E E O'Neil
R S Palmer
G W Papen
S H Proger
H A Rice
D D Scannell
J A Seth
L A Sieracki
S L Skvirsky
E S Smith
Kathleyn S Snow
J W Spellman
A R Staggs
W J Walton
N A Welch
W A White, Jr
G F Wilkins
P R Withington
Marjorie Woodman

NORFOLK SOUTH

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H E Kennard
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C C Lund
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L S McKittrick
Donald Munro
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At this point, Dr. John Curley asked for support of the World Health Organization.

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This report was submitted by the President as informational. It was moved, seconded and voted to approve the report.

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The report was approved as informational.

Committee on National Legislation

This report was approved as informational. At the request of the President, Dr. Hayden said that the letters were printed because of their interest and for the information of the Councilors, that Senator Lodge could not be convinced to vote our way and that Senator Smith of Maine could not be won over. Dr. Allen commented on the excellent job done by the committee during the hot summer. Dr. Hornor called attention to the fact that the year "1938" should be changed to "1948." The amended report was then approved by vote of the committee.

Committee on Arrangements

The Secretary moved that dates and place suggested for the 1950 annual meeting be approved. The motion was seconded and so voted.

Committee on Membership

Dr Pilcher presented the report of the Committee and stated that the recommendation was approved by four of his committee, and that one absentee wished to be recorded as not favoring it. The Secretary moved that the recommendation of the committee be approved. This motion was seconded. The Secretary then reviewed the problem and stated the reasons for the recommendation as printed in the Circular of Advance Information. Dr Fallon said the Committee on Membership would still have as much power as ever. Dr Hornor said the present by-law was written as it is at the request of the Committee on Membership at the time.

Dr Parkhurst questioned the value of only a year and wondered if fellows would sponsor a man after such a short acquaintance. Dr Allen said that by next year most graduates of unapproved schools would have been registered five years. Dr Cook said he thought this a step forward. Dr Allen put the question, and it was so voted.

The Secretary then moved that the report of the Committee on Membership concerning retirements and resignations and deprivations be approved. The motion was seconded. Dr Hubbard said the name of Dr Charlotte A. Stewart should be removed from the list of deprivations because she had paid her dues. With this amendment, the motion was passed.

Committee on Public Health

The report was presented by Dr Ward and was approved, including the recommendation concerning the survey, without discussion, as was the matter of the subcommittee.

Committee on Society Headquarters

In the absence of the chairman, Dr Joseph S. Barr presented the report of the committee and said that with the permission of the President, he would like to present some thoughts of his own as follows:

The problem of planning changes in the physical layout of the Massachusetts Medical Society Headquarters cannot be satisfactorily solved without defining rather carefully the scope of the Society's activities. This not only should embrace the present situation but also should include a careful look into the future. If we assume that the federal Government will, in the near future, be the dominant factor in American medicine, our plans should be modest and tempered by expediency. If, on the other hand, we foresee continuation of our present voluntary system, we are faced with a challenging opportunity. The Massachusetts Medical Society is the logical, in fact the only organization, that can assume a position of active leadership in all phases of the never-ceasing struggle to improve the health of the people of the Commonwealth and of this geographic region.

The postgraduate training program for general practitioners, not only of Massachusetts but also of New England, will need to be expanded far beyond our present efforts in that direction. Television will probably be the new courier to carry the best of modern medical progress directly to the staff of every community hospital, not just once a year but perhaps every month. The community hospitals, the community health center and the general practitioners are key figures, and we must give them every assistance in the fulfillment of their needs. Regional rather than state co-ordination of postgraduate medical programs is obviously of value.

Our relation to Government agencies, federal and state, needs to be realistically reappraised. We must work with these agencies, for Government is now in medicine and will be in it increasingly in the foreseeable future. The Massachusetts Medical Society must actively study public-health problems and assist in solving them. Our relation with the public itself leaves much to be desired. The lay public needs education not only in personal hygiene and home nursing and in the understanding of disease processes, but also in the broader fields of pub-

lic health and medical economics. The Society must assume leadership in the field of lay education and in the dissemination of medical news of interest to the public.

The Headquarters Committee has wrestled for years with the problem of how to house the expanding activities of the Massachusetts Medical Society. There appear to be two possible alternative solutions to the problem. One is to enlarge and alter our present headquarters. The other is to build a new headquarters in a new location. Several surveys have been made and two sets of plans have been independently prepared that would improve what we now have. No adequate study of a new building program has been made. Such a study should be undertaken and completed before a sound basis for decision between these two plans can be reached.

A new building program is an ambitious venture and will require a great deal of careful study. For such a venture to succeed, the co-operation of many existing organizations will be necessary. It is unrealistic to expect that a committee can without assistance prosecute and complete such a study. It is believed that the study can best be undertaken by selecting one person, who, under the direction of the Committee, would devote his full-time efforts to the project. At the end of a limited time, perhaps three months, he should be prepared to submit a preliminary report. If the report indicates beyond reasonable doubt that the project would receive support from other interested organizations and that it is possible to finance a new building program satisfactorily, he should then be authorized to proceed with the preparation of more detailed plans.

Careful study may reveal that a new building program for the Massachusetts Medical Society is completely visionary and impractical. It may, on the other hand, reveal that this program is not only possible but also the only sound solution to our present pressing problems. There are many details and problems that will arise in connection with the proposed study. If someone with the essential initiative and ability is selected and is given proper authorization and assistance, he should be able to submit a concrete report with specific recommendations, something that has not been done previously.

Dr Hornor then made the following statement:

The question is whether the Massachusetts Medical Society should continue to grow steadily by confining its activities to meeting immediate problems to the best of its ability or should look forward to great expansion either alone or in combination. The Committee decided against combining with a nonmedical group, but did not feel capable of making the decision about combining with such organizations as Harvard School of Public Health and Massachusetts Department of Public Health without a more thorough investigation than we felt capable of performing. If the Executive Committee thinks it can answer the question, the Committee on Society Headquarters will be grateful and proceed accordingly; otherwise, we would like paid help who can devote many hours to the problem.

Dr Hornor then made a motion that the recommendation of the committee be approved. The motion was seconded. Thirty-five pages of discussion followed, during which the following points were emphasized: the committee had not accomplished very much for ten years, the committee might do a great deal of the groundwork itself, all parties concerned in the future building plans should be invited to sit in with the committee, the plans of the Library trustees for the enlargement of 8 Fenway should be carefully considered, the plans of the future development of the Society in postgraduate-education programs should be decided, the possibility of interesting a foundation interested in an enlarged program should be considered, the man selected to draw plans should also evaluate the problem as a whole, the treasurer believed that any money expended for the purpose should come out of the general expenses and not the Building Fund.

The President then put the question, and the motion was defeated. Dr Conlin pointed out the difficulties of operating in the cramped quarters at 8 Fenway. Dr Allen said he thought it would be too bad to spend a large sum on 8 Fenway if there was hope that we might have a truly dignified Academy of Medicine. Dr John Curley moved re-

consideration of the motion. This was seconded, and it was so voted.

It was then pointed out in discussion that the Committee was sure that it could not solve the problem without expert advice and help, someone to do the leg work. Dr. Dame asked if the plan to join the Boston Museum of Science had been turned down. Dr. Barr said it had not. Dr. Barr said a policy for the future could not be developed without consultation of a great many people. Dr. Conlin stated that he did not know of any medical society satisfied with present quarters—they were all outgrowing them. Dr. Barr said that any plans developed by an employed person or group would have to be acceptable to the Committee. The President put the original motion again, which was seconded, and it was so voted.

Committee on Industrial Health

In the absence of the chairman, Dr. Henry Marble, the Secretary moved that the recommendation to hold an industrial health conference in Boston on November 16, 1949, be approved. The motion was seconded, and it was so voted without debate.

SPECIAL COMMITTEES

Committee to Meet with the Massachusetts Hospital Association

This report was approved as informational without discussion. Dr. Hornor moved that the Committee be thanked for its fine efforts and be asked to make another report at the February meeting of the Council. The motion was seconded, and it was so voted.

Committee on Postgraduate Medical Education

This report was approved as informational.

Committee on Medical Economics

The report was presented by Dr. Bagnall, who moved the approval of the report. The motion was seconded. Dr. Hornor said he would like to see No. 13 left out of the principles, because he felt the problem was one between a certain school needing help and wishing to get it from the Government. Dr. Bagnall said it was not a state or individual problem because medical schools were educating students for the whole country. Private sources of aid are drying up. Dr. Curley objected to federal control after federal aid. Dr. Bagnall answered that the paragraph stipulates no interference by the Government.

Dr. Allen put the question, and it was carried by a majority of two.

Committee on New England Postgraduate Assembly

This report was approved as informational.

Committee on Diabetes

Dr. Root presented the report and said that now there are 148 units in 40 states taking part in the program. It was hoped to have an exhibit at the Eastern States Exposition. He said industry is very much interested. The most important thing was to get the interest of the doctors and that it would cost some extra money to send them a letter. Dr. Hubbard said Dr. Root should apply to the Committee on Finance. On motion made and seconded, the report was approved without discussion.

Co-ordinating Committee

This report was approved without discussion.

Committee on Publicity Code

In the absence of Dr. Munro, Dr. Hornor presented the report and moved that the code be approved. The motion was seconded. Dr. Conlin outlined the history of the code, how it originally came from the Eye and Ear Infirmary as a hospital code to guide their staff, how it had been reviewed by the Committee on Ethics and Discipline and found not affecting the code of ethics of the Society. It was then referred back to a special committee to write a code applying to all fellows of the Society, and although a little cumbersome, it is spelled out for a purpose. It can be clarified for newspapers and radio at the proposed conference with press and radio.

The President stated the motion, and it was so voted. Dr. Hornor moved approval of the second recommendation to continue the committee. The motion was seconded, and it was so voted.

Dr. Hornor moved approval of the third recommendation, to publish the code in the new booklet on by-laws. The motion was seconded, and it was so voted.

Report of the Meeting of House of Delegates of the American Medical Association

This report was accepted as informational. The Secretary stated that the report of the Committee on Hospitals and the Practice of Medicine (The Hess Committee) had included the report of the Committee on Special Services of the Society and had praised the Massachusetts Medical Society for its valuable contribution. He also said he hoped everyone would read this report in the proceedings of the House of Delegates. Dr. Conlin moved that these remarks be given to the Council in the report of the Executive Committee. The motion was seconded, and it was so voted.

Dr. Fallon moved that the name of the Committee to meet with the Massachusetts Hospital Association be changed to the Committee on Hospitals and Professional Relations. The motion was seconded, and it was so voted.

Advisory Committee for Red Cross Blood Bank

Dr. Lamar Soutter presented the report and said that the Red Cross had to meet the approval and continue under that approval in everything that is done. The program depends greatly on publicity and on the support of the professions for success. The recommendations of the committee fall into three groups: publicity in the *Journal*, telling the doctors how they can help and the training of hospital personnel. It was moved and seconded that the first recommendation be approved. It was so voted.

It was moved that the second recommendation be approved if changed to "that the help of the *Journal* should be enlisted with the following ends in view." The motion was seconded, and it was so voted with the approval of Dr. Soutter.

Dr. Allen ruled that the permission asked for to write to hospitals and district societies for information on how the program is working was not necessary since the committee had that power. Dr. Soutter moved that the Society give its support to the program of training technicians. This motion was seconded and so voted. Dr. Hornor requested that the word "district" be substituted for "county." Dr. Soutter agreed.

Committee on Blue Cross-Blue Shield Problems

Dr. Kichham presented the report and asked permission to change the wording of the report by substituting for lines 17 to 24 on page 32 of the Circular of Advance Information beginning with the word "the" in line 17 and ending with the word "it" on line 24, the following:

It was pointed out that until about a year ago Blue Shield made no payments for medical services rendered to ward service cases, because it was the confirmed policy of the hospitals involved that staff physicians should not bill for such services. During 1948 this policy on the part of several teaching hospitals was altered to the extent that staff groups, but not individual physicians, were permitted to receive payments for third parties, such as Blue Shield and commercial insurance companies, for medical services rendered to service-ward patients. Formal group arrangements were made at two hospitals, and informal group arrangements were made at several other hospitals, after which Blue Shield began making payment to these groups.

Such permission was granted by vote of the committee. Dr. Kichham said that his committee had considered the recommendation at the end of the report, and that the matter of physician enrollment had subsequently been discussed several times without results. He hoped the President would be allowed to refer the subject to an appropriate committee. Dr. Hornor stated that the Committee on Public Relations had previously voted against group enrollment of physicians in Blue Shield.

Dr. Tripp moved that the subject be studied further by this committee which will report to the Council at a later date. The motion was seconded, and it was so voted.

Committee on Arrangements

The Secretary moved that dates and place suggested for the 1950 annual meeting be approved. The motion was seconded and so voted.

Committee on Membership

Dr Pilcher presented the report of the Committee and stated that the recommendation was approved by four of his committee, and that one absentee wished to be recorded as not favoring it. The Secretary moved that the recommendation of the committee be approved. This motion was seconded. The Secretary then reviewed the problem and stated the reasons for the recommendation as printed in the Circular of Advance Information. Dr Fallon said the Committee on Membership would still have as much power as ever. Dr Hornor said the present by-law was written as it is at the request of the Committee on Membership at the time.

Dr Parkhurst questioned the value of only a year and wondered if fellows would sponsor a man after such a short acquaintance. Dr Allen said that by next year most graduates of unapproved schools would have been registered five years. Dr Cook said he thought this a step forward. Dr Allen put the question, and it was so voted.

The Secretary then moved that the report of the Committee on Membership concerning retirements and resignations and deprivations be approved. The motion was seconded. Dr Hubbard said the name of Dr Charlotte A Stewart should be removed from the list of deprivations because she had paid her dues. With this amendment, the motion was passed.

Committee on Public Health

The report was presented by Dr Ward and was approved, including the recommendation concerning the survey, without discussion, as was the matter of the subcommittee.

Committee on Society Headquarters

In the absence of the chairman, Dr Joseph S Barr presented the report of the committee and said that with the permission of the President, he would like to present some thoughts of his own as follows:

The problem of planning changes in the physical layout of the Massachusetts Medical Society Headquarters cannot be satisfactorily solved without defining rather carefully the scope of the Society's activities. This not only should embrace the present situation but also should include a careful look into the future. If we assume that the federal Government will, in the near future, be the dominant factor in American medicine, our plans should be modest and tempered by expediency. If, on the other hand, we foresee continuation of our present voluntary system, we are faced with a challenging opportunity. The Massachusetts Medical Society is the logical, in fact the only organization, that can assume a position of active leadership in all phases of the never-ceasing struggle to improve the health of the people of the Commonwealth and of this geographic region.

The postgraduate training program for general practitioners, not only of Massachusetts but also of New England, will need to be expanded far beyond our present efforts in that direction. Television will probably be the new courier to carry the best of modern medical progress directly to the staff of every community hospital, not just once a year but perhaps every month. The community hospitals, the community health center and the general practitioners are key figures, and we must give them every assistance in the fulfillment of their needs. Regional rather than state co-ordination of postgraduate medical programs is obviously of value.

Our relation to Government agencies, federal and state, needs to be realistically reappraised. We must work with these agencies, for Government is now in medicine and will be in it increasingly in the foreseeable future. The Massachusetts Medical Society must actively study public-health problems and assist in solving them. Our relation with the public itself leaves much to be desired. The lay public needs education not only in personal hygiene and home nursing and in the understanding of disease processes, but also in the broader fields of pub-

lic health and medical economics. The Society must assume leadership in the field of lay education and in the dissemination of medical news of interest to the public.

The Headquarters Committee has wrestled for years with the problem of how to house the expanding activities of the Massachusetts Medical Society. There appear to be two possible alternative solutions to the problem. One is to enlarge and alter our present headquarters. The other is to build a new headquarters in a new location. Several surveys have been made and two sets of plans have been independently prepared that would improve what we now have. No adequate study of a new building program has been made. Such a study should be undertaken and completed before a sound basis for decision between these two plans can be reached.

A new building program is an ambitious venture and will require a great deal of careful study. For such a venture to succeed, the co-operation of many existing organizations will be necessary. It is unrealistic to expect that a committee can without assistance prosecute and complete such a study. It is believed that the study can best be undertaken by selecting one person, who, under the direction of the Committee, would devote his full time efforts to the project. At the end of a limited time, perhaps three months, he should be prepared to submit a preliminary report. If the report indicates beyond reasonable doubt that the project would receive support from other interested organizations and that it is possible to finance a new building program satisfactorily, he should then be authorized to proceed with the preparation of more detailed plans.

Careful study may reveal that a new building program for the Massachusetts Medical Society is completely visionary and impractical. It may, on the other hand, reveal that this program is not only possible but also the only sound solution to our present pressing problems. There are many details and problems that will arise in connection with the proposed study. If someone with the essential initiative and ability is selected and is given proper authorization and assistance, he should be able to submit a concrete report with specific recommendations, something that has not been done previously.

Dr Hornor then made the following statement:

The question is whether the Massachusetts Medical Society should continue to grow steadily by confining its activities to meeting immediate problems to the best of its ability or should look forward to great expansion either alone or in combination. The Committee decided against combining with a nonmedical group, but did not feel capable of making the decision about combining with such organizations as Harvard School of Public Health and Massachusetts Department of Public Health without a more thorough investigation than we felt capable of performing. If the Executive Committee thinks it can answer the question, the Committee on Society Headquarters will be grateful and proceed accordingly; otherwise, we would like paid help who can devote many hours to the problem.

Dr Hornor then made a motion that the recommendation of the committee be approved. The motion was seconded. Thirty-five pages of discussion followed, during which the following points were emphasized: the committee had not accomplished very much for ten years, the committee might do a great deal of the groundwork itself, all parties concerned in the future building plans should be invited to sit in with the committee, the plans of the Library trustees for the enlargement of 8 Fenway should be carefully considered, the plans of the future development of the Society in postgraduate-education programs should be decided, the possibility of interesting a foundation interested in an enlarged program should be considered, the man selected to draw plans should also evaluate the problem as a whole, the treasurer believed that any money expended for the purpose should come out of the general expenses and not the Building Fund.

The President then put the question, and the motion was defeated. Dr Conlin pointed out the difficulties of operating in the cramped quarters at 8 Fenway. Dr Allen said he thought it would be too had to spend a large sum on 8 Fenway if there was hope that we might have a truly dignified Academy of Medicine. Dr John Curley moved re-

consideration of the motion. This was seconded, and it was so voted.

It was then pointed out in discussion that the Committee was sure that it could not solve the problem without expert advice and help, someone to do the leg work. Dr Dame asked if the plan to join the Boston Museum of Science had been turned down. Dr Barr said it had not. Dr Barr said a policy for the future could not be developed without consultation of a great many people. Dr Conlin stated that he did not know of any medical society satisfied with present quarters—they were all outgrowing them. Dr Barr said that any plans developed by an employed person or group would have to be acceptable to the Committee. The President put the original motion again, which was seconded, and it was so voted.

Committee on Industrial Health

In the absence of the chairman, Dr Henry Marble, the Secretary moved that the recommendation to hold an industrial health conference in Boston on November 16, 1949, be approved. The motion was seconded, and, it was so voted without debate.

SPECIAL COMMITTEES

Committee to Meet with the Massachusetts Hospital Association

This report was approved as informational without discussion. Dr Hornor moved that the Committee be thanked for its fine efforts and be asked to make another report at the February meeting of the Council. The motion was seconded, and it was so voted.

Committee on Postgraduate Medical Education

This report was approved as informational.

Committee on Medical Economics

The report was presented by Dr Bagnall, who moved the approval of the report. The motion was seconded. Dr Hornor said he would like to see No. 13 left out of the principles, because he felt the problem was one between a certain school needing help and wishing to get it from the Government. Dr Bagnall said it was not a state or individual problem because medical schools were educating students for the whole country. Private sources of aid are drying up. Dr Curley objected to federal control after federal aid. Dr Bagnall answered that the paragraph stipulates no interference by the Government.

Dr Allen put the question, and it was carried by a majority of two.

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This report was approved as informational.

Committee on Diabetes

Dr Root presented the report and said that now there are 148 units in 40 states taking part in the program. It was hoped to have an exhibit at the Eastern States Exposition. He said industry is very much interested. The most important thing was to get the interest of the doctors and that it would cost some extra money to send them a letter. Dr Hubbard said Dr Root should apply to the Committee on Finance. On motion made and seconded, the report was approved without discussion.

Co-Ordinating Committee

This report was approved without discussion.

Committee on Publicity Code

In the absence of Dr Munro, Dr Hornor presented the report and moved that the code be approved. The motion was seconded. Dr Conlin outlined the history of the code, how it originally came from the Eve and Ear Infirmary as a hospital code to guide their staff, how it had been reviewed by the Committee on Ethics and Discipline and found not affecting the code of ethics of the Society. It was then referred back to a special committee to write a code applying to all fellows of the Society, and although a little cumbersome, it is spelled out for a purpose. It can be clarified for newspapers and radio at the proposed conference with press and radio.

The President stated the motion, and it was so voted. Dr Hornor moved approval of the second recommendation to continue the committee. The motion was seconded, and it was so voted.

Dr Hornor moved approval of the third recommendation, to publish the code in the new booklet on by-laws. The motion was seconded, and it was so voted.

Report of the Meeting of House of Delegates of the American Medical Association

This report was accepted as informational. The Secretary stated that the report of the Committee on Hospitals and the Practice of Medicine (The Hess Committee) had included the report of the Committee on Special Services of the Society and had praised the Massachusetts Medical Society for its valuable contribution. He also said he hoped everyone would read this report in the proceedings of the House of Delegates. Dr Conlin moved that these remarks be given to the Council in the report of the Executive Committee. The motion was seconded, and it was so voted.

Dr Fallon moved that the name of the Committee to meet with the Massachusetts Hospital Association be changed to the Committee on Hospitals and Professional Relations. The motion was seconded, and it was so voted.

Advisory Committee for Red Cross Blood Bank

Dr Lamar Soutter presented the report and said that the Red Cross had to meet the approval and continue under that approval in everything that is done. The program depends greatly on publicity and on the support of the professions for success. The recommendations of the committee fall into three groups: publicity in the *Journal*, telling the doctors how they can help and the training of hospital personnel. It was moved and seconded that the first recommendation be approved. It was so voted.

It was moved that the second recommendation be approved if changed to "that the help of the *Journal* should be enlisted with the following ends in view." The motion was seconded, and it was so voted with the approval of Dr Soutter.

Dr Allen ruled that the permission asked for to write to hospitals and district societies for information on how the program is working was not necessary since the committee had that power. Dr Soutter moved that the Society give its support to the program of training technicians. This motion was seconded and so voted. Dr Hornor requested that the word "district" be substituted for "county." Dr Soutter agreed.

Committee on Blue Cross-Blue Shield Problems

Dr Kickham presented the report and asked permission to change the wording of the report by substituting for lines 17 to 24 on page 32 of the Circular of Advance Information beginning with the word "the" in line 17 and ending with the word "fit" on line 24, the following:

It was pointed out that until about a year ago Blue Shield made no payments for medical services rendered to ward service cases, because it was the confirmed policy of the hospitals involved that staff physicians should not bill for such services. During 1948 this policy on the part of several teaching hospitals was altered to the extent that staff groups, but not individual physicians, were permitted to receive payments for third parties, such as Blue Shield and commercial insurance companies, for medical services rendered to service-ward patients. Formal group arrangements were made at two hospitals, and informal group arrangements were made at several other hospitals, after which Blue Shield began making payment to these groups.

Such permission was granted by vote of the committee. Dr Kickham said that his committee had considered the recommendation at the end of the report, and that the matter of physician enrollment had subsequently been discussed several times without results. He hoped the President would be allowed to refer the subject to an appropriate committee. Dr Hornor stated that the Committee on Public Relations had previously voted against group enrollment of physicians in Blue Shield.

Dr Tripp moved that the subject be studied further by this committee which will report to the Council at a later date. The motion was seconded, and it was so voted.

Dr Fallon asked for clarification of the meaning of the words "judicious application by the medical profession" on page 33, line 9. Dr Conlin said that for the doctor to charge an extra fee for these patients might be warranted in some cases, but that to do so would demand good judgment if severe criticism were not to be brought against the doctor and Blue Shield. On a motion duly made and seconded, the report as amended was approved.

Advisory Committee to Woman's Auxiliary

Dr Conlin presented the report as informational and it was approved by the committee as such.

Dr Conlin said that the Harvard School of Public Health is to conduct a survey of multiple sclerosis in the State with funds supplied by the National Society for Multiple Sclerosis and that approval of this survey had been obtained by a telephone vote of the Committee on Public Health. It should have been included in the report of that committee. Dr Conlin made a motion that a recommendation to approve the survey be added as an amendment to the report of the Committee on Public Health. The motion was seconded, and it was so voted.

Dr Conlin made a motion that a recommendation endorsing the Boston Chest X-ray Program be appended to the Report of the Committee on Public Health. This motion was seconded, and it was so voted.

On motion duly made and seconded, the meeting adjourned at 6:50 p.m.

H QUIMBY GALLUPE, *Secretary*

APPENDIX NO 3

REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

The meeting of the Public Relations Committee of the Massachusetts Medical Society was held at the Harvard Club at 6:00 p.m. on July 27, 1949. President Arthur W. Allen was in the chair, there were present 15 out of the 18 representatives of the district societies. Dr H. Quimby Gallupe, secretary of the Massachusetts Medical Society, and Dr John F. Conlin, director of medical education and information, were also present.

Dr John F. Conlin presented to the Committee the desirability of a medical-press-radio conference to be held in the latter part of October, 1949. To this meeting would be invited, in addition to the medical profession, representatives of various hospitals and members of the press and radio. He felt that by and large the press is favorable to organized medicine. There is, however, some doubt in the minds of the press about possible sources of authentic information regarding medical subjects and medical information, such as the value of new drugs and recent medical advances. It was his opinion that newspapermen are just as ethical as members of the medical profession, and that members of the press are anxious to disseminate accurate information provided sources for the obtaining of such accurate information are available to them. It was Dr Conlin's contention that the first such conference should be held in Boston and later be decentralized to the various district societies in order that there might be such sources of authentic information as the local press might desire. It was unanimously voted by the members of the Committee that such a conference be held.

It was suggested by the Committee at its meeting on August 4, 1948, and later approved by the Council, that a health exhibit should be organized in the fall of 1949. Inasmuch as plans could not be completed for such a program, the Committee unanimously voted to postpone action indefinitely.

Dr John F. Conlin called to the Committee's attention that some states were recognizing laymen for meritorious or distinguished service in the support of public health and good medicine. It was felt that such a program wherever initiated stimulated good public relations. Many laymen or groups of laymen have rendered invaluable service to the progress of medicine by their energetic efforts in its behalf. Therefore, the Committee unanimously endorsed the following resolutions:

That the Council empower the Committee on Public Relations to award some layman or group of laymen a citation for outstanding service to medical progress.

That the Committee shall make not more than three such citations annually.*

Dr Conlin reviewed the work that has been completed with reference to the national education campaign against compulsory health insurance. He emphasized that although there seems to be no immediate danger that the Administration's compulsory health bill will be passed, it was apparent that complacency and inactivity on the part of the medical profession might be disastrous. Efforts to perfect the machinery of the present organization must continue during the coming months. Emphasis was placed upon the necessary work to be carried on by the district co-ordinating committees with reference to the "Tell it to Twenty" portion of the Massachusetts campaign. A strong speakers' bureau should be developed in each district in which not only does the medical profession take part, but also competent and willing lay speakers are encouraged to present organized medicine's point of view regarding the Administration's health bill.

HAROLD R. KURTH, M.D., *Secretary*

*The recommendation to name the lay award "The Lemuel Shattuck Award" was amended by the Council to read "The Massachusetts Medical Society Citation for Outstanding Contributions to Medical Progress."

APPENDIX NO 4

REPORT OF THE COMMITTEE ON TAX-SUPPORTED MEDICAL CARE

The committee on Tax-Supported Medical Care has not met. The chairman of the committee has tried to get help on the questions referred to the committee at the last meeting of the Council from the Commissioner of Public Welfare of the Commonwealth of Massachusetts. Mr. Patrick Tompkins, the commissioner, has postponed any meeting with the members of the committee until after the legislature has prorogued. The committee will continue to work on this problem.

WILLIAM W. BABSON, M.D.

DONALD HIGHT, M.D.

FRANCIS P. MCCARTHY, M.D.

ALBERT A. HORNOR, M.D., *Chairman*

APPENDIX NO 5

REPORT OF THE COMMITTEE ON LEGISLATION

A meeting of the Committee on Legislation was held at the Harvard Club on June 24, 1949. The meeting was called to order by President Arthur W. Allen, who nominated the following men as members of the Executive Committee: Dr Alfred M. Glickman, Dr William E. Browne, Dr Solomon L. Skvirsky, and Dr John Butts.

Dr Allen's nominations were approved by the Committee. Dr Skvirsky stated that he would be unable to serve as secretary of the Committee. By vote of the Committee his resignation was accepted, and Dr Daniel F. Gallery, of Bristol South, was elected.

After some discussion it was voted that the Executive Committee be granted power to act on legislative matters in any case of emergency.

The main business of the meeting was a discussion of the cash sickness bill No. 2591, the passage of which had been urged by the Governor in his inaugural address. Mr. Charles Dunn stated that the Society should prepare a brief explaining its stand on this bill. On the completion of the discussion, the Committee voted unanimously in opposition to the bill, and Mr. Dunn was authorized to state in the brief that the legislative councilors of the Massachusetts Medical Society regret that they cannot approve the bill in its present form.

At the suggestion of the chairman, Dr David L. Belding, Dr Charles G. Hayden and Dr John F. Conlin were asked to assist Mr. Dunn in the writing of the brief. The meeting adjourned at 10:00 p.m.

DAVID L. BELDING, M.D., *Chairman*

The brief as presented to the Committee on Ways and Means of the Legislature meeting in Executive Session was as follows:

Statement of the Massachusetts Medical Society on House No. 2591, the Cash Sickness Compensation Bill,

for the Committee on Ways and Means of the Massachusetts General Court.

The Massachusetts Medical Society finds itself not in complete agreement with House No 2591, the Cash Sickness Compensation Bill, as it now stands.

This bill has been carefully studied by the Society since printed copies became available. It is not our purpose to single out points we would praise or condemn as private citizens and voters interested in the broad problems of the public health.

Our principle function as a medical society is to view this, as all other legislation pertaining to health, as working for or against the best possible standards of medical progress and the mental and physical health of the public.

Under this bill as drawn the physician is held responsible for the medical operation of the sickness compensation plan. The claimant for benefits must have filed a physician's certificate (*Sec 7 (a) (f)*) and, "if directed to do so by the director, (shall) have submitted to a medical examination for the purpose of determining his sickness" (*idem*).

In practice this requirement would charge practicing physicians not only with administrative responsibilities but with under-writing responsibility as well. E. H. O'Connor, managing director, Insurance Economics System of America, has stated, "As these state plans begin to expand, as is evident from legislative bills introduced in Rhode Island, California and New Jersey, more benefits will be paid and the cash sickness benefits of a state fund must be protected. It will naturally follow that the state will be forced to set up rules and regulations for the certification of claimants."

Solvency of a state fund might be protected if it were possible to determine ability to work in all instances through promulgation of rules, and regulations and the application of existing medical knowledge. Every physician knows there are many instances where it is absolutely impossible to determine medically whether a person is or is not able to work.

This is particularly true in cases of mental illness. The definition of "sickness" (*Sec 3 (m)*) contains the words

"because of his physical or mental condition, he is unable to perform his regular or customary work." It was stated in Federal Security Administrator Oscar R. Ewing's report to the President that from 30 to 50 per cent of all persons consulting doctors have complaints due at least in part to emotional disorders. For the evaluation of these complaints it is stated 4500 psychiatrists are available in this country where some 15,000 are needed.

From the point of view of the medical profession, charged with the responsibility of certification and professional administration, it cannot be too much stressed that this program concerns itself essentially with temporary disability. Experience has emphasized the importance of adequate administrative control for the successful operation of such plans. We wish to stress that the evaluation of conditions of temporary disability depends upon factors which are at best 50 per cent subjective.

The dangers to the solvency of the cash sickness compensation fund from malingering have been recognized by the architects of this bill. "He (the director) shall also publicize the potential results of malingering" (*Section 18*). In view of what has been said above concerning the subjective factors of temporary disability it must be made clearly apparent that merely designating the physician as the policeman is not the answer. There are no magic tests for the evaluation of purely subjective symptoms.

For the 6750 physician fellows of the Massachusetts Medical Society we feel we can promise full co-operation within the code of ethics of the Society and of the American Medical Association within the limitations previously noted. We point out, however, that no criteria for diagnoses are established within the bill and there is no provision for a medical advisory board to assist in this and other important functions under the bill.

The bill defines a "physician" (*Section 3 (j)*) as "an individual licensed to practice medicine or dentistry under the laws of this or any other state." For some 2500 physicians licensed to practice in Massachusetts the added ethical controls over fellows of the Massachusetts Medical

Society are absent. For them the basic legal controls of malpractice laws are the limits to which they can be held.

Under *Section 8 Claims and Appeals (e)* provision is made for calling as an expert witness any medical adviser appointed by the director. There is no provision made for establishing the qualifications of such experts.

In view of the tremendous responsibilities placed upon the individual physician and upon the medical profession in the administration of this plan, we seriously question the absence of the physician's voice in the set-up for administrative control.

This defect is the more notable since *Section 12 Penalties* states, "Any person convicted of a violation of any provision of this chapter or of a violation of any order, rule or regulation of the director or of the division made under the authority of any provision of this chapter the punishment for which is not otherwise provided, shall be punished by a fine or not more than fifty dollars for the first offense, and for any subsequent offense within a period of two years immediately following his final conviction of a like offense by a court of the Commonwealth, shall be punished by a fine of not less than fifty dollars nor more than two hundred dollars, or by imprisonment for not more than two years, or both."

Respectfully submitted for the President and Fellows of the Massachusetts Medical Society

/s/ JOHN F. COLLIN, M.D.

JOHN F. COLLIN, M.D.

Director of Medical Information and Education

APPENDIX NO 6

REPORT OF THE SUBCOMMITTEE ON NATIONAL LEGISLATION

The Subcommittee on National Legislation met during the annual meeting of the Society at Worcester on two occasions to consider the provisions of a mimeographed bill sent by Representative Herter to the Society for criticism prior to introduction into the Congress. The Subcommittee's criticism of this bill, which was subsequently introduced by Mr. Herter and others in the House (H.R. 4918) and by Senators Flanders and Dies in the Senate (S. 1970), is appended hereto.

After the annual meeting the Subcommittee met with the Committee on Medical Economics on three occasions, and it is anticipated that there will be additional joint meetings of these two groups. National legislation and medical economics are so inextricably bound together that it seems judicious for two committees independently to consider the problems involved.

Letters expressing opposition to extension of the Social Security Act to cover physicians (H.R. 2895) and opposition to the inclusion of health and medical functions in a proposed Department of Welfare (Reorganization Plan No. 1 of 1949) were sent to all the Massachusetts senators and representatives in Congress as well as to the committee hearing the proposals. Copies of these letters are appended hereto.

When Reorganization Plan No. 1 came to vote in the Senate, Senator Saltonstall voted against it and Senator Lodge voted for it. Senator Lodge explained his action on the grounds that the Hoover Commission had recommended the establishment of a Department of Welfare and that he (Lodge) was not convinced that once such a department was established, it would be virtually impossible to remove its health and medical functions.

The chairman of the Subcommittee attended two meetings of the Committee on Legislation held subsequent to the annual meeting.

ELMER S. BAGNALL, M.D.

DAVID L. BELDING, M.D.

VLADE GETTING, M.D.

AUGUSTUS THORNDIKE, M.D.

WILLIAM H. SWEET, M.D.

CHARLES G. HAYDEN, M.D., *Chairman*

May 26, 1940

Hon. Christian A. Herter

House of Representatives

Washington 25, D. C.

My dear Congressman:

The Subcommittee on National Legislation of the Massachusetts Medical Society sincerely appreciates your in-

terest in the health of the Nation and the people of Massachusetts. It also appreciates the opportunity afforded to scrutinize the proposed National Health Act of 1949.

Because it is impossible in a few days to analyze thoroughly all the implications of a bill of this type, the Subcommittee is submitting herewith a few preliminary observations for your consideration. (See attachment.)

In general, it appears that this bill endeavors to establish a comprehensive system of medical and hospital care, utilizing voluntary prepayment plans and avoiding compulsion insofar as the potential subscriber is concerned. There is no mention made of employer contribution nor is the method of financing clearly defined. Ostensibly, subscribers would pay in accordance with their ability, and pools of reserves would be established to subsidize plans overburdened with poor risks. It seems that the chief financial burden would be carried by those with greater-than-average income who would pay in much more than they would receive in the form of benefits.

The plan visualized is not an insurance program because it offers services which do not lend themselves to actuarial determinations. Just how those persons and institutions who would render the services are to be included in the program and compensated for their efforts is not clear. While the bill does not say so explicitly, there are indications that it is an attempt to synthesize prepayment and group practice and extend the result nationwide. While such an amalgamation may have transcending merit, the available evidence at this time is far from conclusive.

From an administrative standpoint, the bill is replete with conflicting interests and duties vested in several boards, authorities and councils.

It is the opinion of the Subcommittee that this bill, if passed, would ultimately result in the absorption by the Federal Government of voluntary, non-profit, prepayment medical and hospital care plans.

Although much is currently being voiced and written about the health of the nation and the availability and cost of medical care, no one has yet been able to define adequate medical care in terms that are practical and realistic. Until this is done and until there is general agreement on basic facts and concepts, it will be impossible to properly evaluate the problem, let alone suggest a reasonable answer. Therefore we propose that an impartial body patterned after the Hoover Commission be constituted on the National level to correlate the activities of similar Commissions established in the several States, that these Commissions be given ample opportunity to establish facts and evaluate concepts, and that upon completion of their tasks all interested parties sit down together and work out the kind of medical care that will adequately serve the needs of a free people.

Respectfully yours,

*By direction of the President of
Massachusetts Medical Society,
ARTHUR W. ALLEN, M.D.
CHARLES G. HAYDEN, M.D., Chairman
Subcommittee on National Legislation*

PRELIMINARY OBSERVATIONS CONCERNING THE PROPOSED "NATIONAL HEALTH ACT OF 1949"

By the Subcommittee on National Legislation of the
Massachusetts Medical Society

1 The provision that the Surgeon General, subject to approval of the Federal Security Administrator, shall make such administrative regulations and perform such other functions as he finds necessary to carry out the provisions of Title VII is in keeping with current practice. We believe, however, that the medical activities of the Federal government should be co-ordinated in an independent agency directly responsible to the President.

Furthermore, it appears that, except for certain loans, the medical care aspects of this program are to be financed by premiums obtained from subscribers in accordance with their ability to pay. If this is so, regulatory supervision by the Federal government without financial participation might well be questioned.

2 The provision that the Federal Health Council shall be composed of persons who are not professionally engaged in the provision of health services would seem to

be injudicious. It is our feeling that such a body should, in its own interest and that of the public, include persons actually engaged in the provision of health services.

3 The list of Personal Health Services to be provided contains many services which are not insurable because they are subject to serious abuse. In order to provide all the services listed it would appear to be necessary to alter fundamentally the existing pattern of medical, hospital and related practice. The bill does not state how this is to be accomplished.

4 The term, "licensed physicians" would seem to include chiropractors, osteopaths, and others, if licensed by the State. Only fully qualified physicians and surgeons should be allowed to participate.

5 The restrictions placed upon the organization and operation of Co-operating Prepayment Health Service Plans would, in our opinion, result in the abandonment of such plans by just those conscientious and able citizens who should be on the governing boards. For example:

a Benefits offered must be within limits authorized by the State's program.

b Contracts must be approved by the Health Region Authority.

c Enrollment will be limited by the Health Region Authority which will also determine the mechanism of enrollment (individual, group, etc.).

d Reserve requirements will be established by the State Health Council.

e Adjustments in subscription charges must be made in certain instances as required by the State Plan.

f Subscription charges must be fixed in terms of subscriber's family income.

g Rules and regulations will be determined by the Surgeon General, the State Agency, the State Health Council, and the Health Region Authorities.

h Selection Factor will be determined by the Surgeon General.

6 The provision that the State Plan shall be administered by a single State Agency subject to the powers of the State Health Council and Health Region Authorities (and the Surgeon General) would seem to make for divided authority and inefficient administration. The possibility that two or more contiguous states may be involved is subject to this same criticism. Also, the lack of correlation between the proposed agencies and those already in existence (State and local health departments, etc.) might well result in conflict, overlapping, inefficiency and waste of funds.

7 The provisions that the Health Region Authority shall be composed of persons who do not hold positions of administrative responsibility for any health program or other activity of the State or any political subdivision thereof, and who are not professionally engaged in the provision of health or medical services again bars just those persons whose knowledge and experience would be invaluable.

8 The requirement that each Health Service District include within its area a four-year medical college would seem to impose unrealistic geographic arrangements.

9 The requirement that the State Health Council determine and prescribe the kinds of personal health services to be provided and the reserve requirements therefor, circumvents State Insurance Departments which are already authorized to make such determinations in most States.

10 The provision that prepayment health service plans shall subsidize medical schools is unique. As the program visualized is not compulsory, the burden of subsidization would fall on subscribers alone and not on the general public, all of whom should contribute if governmental subsidy is necessary and desirable.

11 Fixing of subscription charges in terms of a percentage of the subscriber's family income would seem to introduce serious administrative difficulties. How, for instance, is family income to be determined in those instances where more than one member of the family is employed, or where there is income other than wages or salary?

12 The provision for creation of a Study and Planning Commission has merit. It is our opinion that a Commission similar to the Hoover Commission should be constituted in every State and that the activities of these

several State Commissions should be correlated by a similar Commission on the Federal level. Furthermore, we believe that until such time as these Commissions have submitted their findings and recommendations, legislation in this field should be delayed.

13 We favor in principle extension of the hospital construction program. Because of the limited time available, that portion of the bill dealing with this subject was not analyzed.

14 We favor in principle establishment of local public health units. Because of the limited time available, that portion of the bill dealing with this subject was not analyzed.

July 6, 1949

Senator Henry Cabot Lodge, Jr
Senate Office Building
Washington, D C.

Dear Senator Lodge

There are two social security bills before the House Ways and Means Committee certain provisions of which, if enacted into law, would intimately involve the medical profession. These are H R. 2892 and H R. 2893.

As originally written, H R. 2892 contained a provision which would institute medical assistance for certain categories of indigents. We shall reserve our comments on this provision until such time as we may have the opportunity of examining the revised bill.

H R. 2893, as revised, is reliably reported to contain a provision broadening the coverage of the Social Security Act to include most self-employed persons but excluding farmers. A tax of perhaps 2½ per cent on income up to \$4200 or \$4800 would be levied for the purpose of providing old-age benefits at age 65 to those self-employed who at that age retire from business as well as cash benefits for permanent disability.

Because few physicians retire at age 65 and because virtually complete retirement is necessary to qualify for an old-age pension, physicians would be compelled to contribute for years to a fund from which few if any would ever derive benefits. We are, therefore, opposed to extension of the Social Security Act to include physicians.

Respectfully submitted

By Direction of the President

CHARLES G HAYDEN, M D, *Chairman*
Subcommittee on National Legislation

July 21, 1949

Senator Joseph R. McCarthy
Senate Committee on Expenditures in the Executive Offices
Senate Office Building
Washington, D C.

Dear Senator McCarthy

On June 20, 1949, President Truman, exercising authority delegated to him in Public Law 109, submitted to the Congress Reorganization Plan No 1. Under this Plan a Department of Welfare will be created to take over and perform the functions and conduct the programs now administered by the Federal Security Agency. Reorganization Plan No 1 will automatically go into effect on August 19, 1949 if Congress is still in session on that date or unless prior to that date either House of Congress passes a simple resolution against it by the affirmative vote of a majority of the authorized membership of that House.

The Massachusetts Medical Society opposes the inclusion of federal health and medical functions in a Department of Welfare. Instead, it has for some time favored the creation of a Department of Health or, if such is not feasible at this time, the creation of an independent federal agency similar to the United Medical Administration recently recommended by the Hoover Commission. The compelling arguments for a United Medical Administration as elaborated by the Hoover Commission are well known and need not be recounted here.

When President Truman submitted Reorganization Plan No 1, he stated that the creation of a Department of Welfare, including health and medical functions, would not in any way interfere with the presentation of additional reorganization plans such as one establishing a

United Medical Administration. However, Federal Security Administrator Oscar R. Ewing is now on record as being opposed to the removal of health and medical functions from the Federal Security Agency and, inferentially, from the proposed Department of Welfare. The Massachusetts Medical Society believes that once federal health and medical functions are lodged in a Department of Welfare, it will be next to impossible to remove them.

In the interest of economy and efficiency, the Federal Security Agency (Administration) has been subjected to several reorganizations. The Reorganization Act of 1939 was designed to, "reduce expenditures, increase efficiency, consolidate agencies according to major purposes, reduce the number of agencies by consolidating those having similar functions and by abolishing such as may not be necessary, and to eliminate overlapping and duplicating of efforts." The Reorganization Act of 1946 had similar purposes. It changed the Federal Security Agency (Administration) from a holding company with a small staff and a small budget to an operating agency which has burgeoned to incredible proportions. Prior to 1946, there existed three component bureaus—one each for health, education, and social security, now there exists a single agency headed by an administrator with a group of assistants. In 1939 there were five top administrative jobs in the bureaus dealing with health, education, and social security. These jobs paid about \$10,000 each and were held by the Surgeon General of the Public Health Service, the Commissioner of Education, and the three members of the Social Security Board. At the present time (1950 budget) provision is made for a Federal Security Administrator at \$12,000, three assistant administrators at \$10,000 each, nine more officials at \$10,000 each, four at more than \$9900 each, and six at over \$9000, or a total of twenty-three positions at over \$9000 each—and these only include persons in the office of the administrator. When the three-person Social Security Board was abolished and replaced by a Commissioner of Social Security, other positions were created for the remaining two members of the Board.

In 1946, prior to reorganization, Federal Security Administration expenditures were \$743,000,000. In 1946, following reorganization, they jumped to \$928,000,000. In 1948 they were \$1,028,000,000, and in 1949, \$1,370,000,000. In 1950 they will be \$1,511,000,000 under existing legislation and \$1,897,000,000 under proposed legislation.

Whether the previous reorganizations of the Federal Security Agency (Administration) have accomplished the purposes intended by the Congress is debatable, but that they have resulted in a serious potential concentration of power and influence over the daily lives of a significant segment of the population of this Nation seems beyond question.

The attitude of Federal Security Administrator Ewing toward the medical profession is well known and need not be elaborated here. Inasmuch as Mr. Ewing would no doubt become the first Secretary of Welfare, his attitude, corresponding as it does with the attitude of the present Minister of Health in England, Aneurin Bevan, is not likely to inspire confidence or a will to co-operate on the part of the medical profession in the solution of the intimate problems of medical care.

Respectfully submitted

By direction of the President

CHARLES G HAYDEN, M D, *Chairman*
Subcommittee on National Legislation

August 10, 1949

Senator Henry Cabot Lodge, Jr
Senate Office Building
Washington, D C.

Dear Senator Lodge

In a final attempt to dispel any misunderstanding in regard to the Hoover Commission's recommendations as they relate to Reorganization Plan No 1, the following quotations from the report of the Voorhees Task Force and the Hoover Commission itself are respectfully presented.

*"Task Force Report on Federal Medical Services (Appendix 0)
Prepared for
The Commission on Organization of the Executive Branch
of the Government
January, 1949*

"According to your chairman's instructions, we have proceeded upon the assumption that the Commission will recommend a new cabinet-level department embracing health, education, and security, in which the broad field of health will be one of the three major functions, also that standard Government nomenclature below the department level will be 'bureau' and thereafter 'division'. We, therefore, describe the health organization which we propose as the National Bureau of Health in such new department

"The above instructions excluded from our consideration the question as to whether a separate Cabinet department would be established for health alone, as urged by professional groups. However, should this be done, the organization which we are proposing would be adapted to such plan with only a few changes in nomenclature" (Page xix)

*"Task Force Report on Federal Medical Services
(Supplement to Appendix 0)
Prepared for
The Commission on Organization of the Executive Branch
of the Government
March 1949*

"As our committee had been instructed to assume that any consolidated health organization would be a part of a new cabinet-level department embracing health, education and security, which the Commission would recommend, our main report contained on page 1 the following statement 'The above instructions excluded from our consideration the question as to whether a separate cabinet department would be established for health alone, as urged by professional groups. However, should this be done, the organization which we are proposing would be adapted to such plan with only a few changes in nomenclature'

"Thus, we answered in the affirmative the question as to whether the organization, which we originally designated as the National Bureau of Health, could function as an independent department or agency

"It remains to consider whether such an alternative would be preferable. This question has been fully considered by our committee, and we have reached the conclusion that such an independent organization would be preferable to placing this function in a larger department, as the Commission originally proposed" (Page 1)

*"Reorganization of Federal Medical Activities
A report to the Congress by the Commission on Organization
of the Executive Branch of the Government
March, 1949*

"Recommendation No 1 To accomplish these purposes, the Commission recommends the establishment of a United Medical Administration into which would be consolidated most of the large-scale activities of the Federal Government in the fields of medical care, medical research, and public health (in which we include preventive medicine)" (Page 2)

Although the Hoover Commission in another report advocated the establishment of a Department of Welfare, it is clearly the intent of the above recommendations that federal health and medical services should be excluded from such a Department.

The Massachusetts Medical Society has taken no stand in regard to the establishment of a Department of Welfare from which federal health and medical functions would be excluded. It is, however, opposed to the establishment of a Department of Welfare which, contrary to the well substantiated recommendations of the Hoover Commission, would include federal health and medical functions

Respectfully submitted
By direction of the President
CHARLES G HAYDEN, M D, Chairman
Subcommittee on National Legislation

August 11, 1949

Senator Henry Cabot Lodge
Senate Office Building
Washington 25, D C

Dear Senator Lodge

I have tried, without success to date, to achieve an estimate of the amount of money which might be saved were a United Medical Administration established. If I come upon this information prior to the end of next week, I shall send it to you by wire

At the moment all I can say is that it seems likely that Congress would have better control of appropriations for health and medical functions if these functions were consolidated instead of being scattered throughout some forty odd divisions and bureaus as is now the case and as they would continue to be scattered under proposed Reorganization Plan No 1

Respectfully submitted
By direction of the President
CHARLES G HAYDEN, M D, Chairman
Subcommittee on National Legislation

August 15, 1949

Senator Leverett A Saltonstall
Senate Office Building
Washington, D C

Dear Senator Saltonstall

The Massachusetts Medical Society believes that once federal health and medical functions are lodged in a Department of Welfare, it will be next to impossible to remove them for the following reasons

1 Federal Security Administrator Oscar R Ewing, who, as payment for his services during the last Presidential campaign, would no doubt be the first Secretary of Welfare, has testified that he will resist the removal of health and medical services from such a Department

2 The President in his letter transmitting Reorganization Plan No 1 and in his recent letter to Vice President Barkley studiously avoided mentioning his intentions in regard to the establishment of a United Medical Service. It would have been an easy matter for him to have stated flatly that, subsequent to the establishment of a Department of Welfare, he would introduce a plan designed to remove health and medical functions

3 It is a well-known fact that it is much easier to exclude functions from a department or agency before it is established than to remove functions later. The anomalous autonomy of the Children's Bureau is an excellent illustration of this point

4 Elevation of the Federal Security Administration as is will accomplish nothing that is not already capable of accomplishment

5 At the present time forty different federal agencies furnish some degree of medical care to 24,000,000 persons. It would seem logical that first priority be given to this wasteful and extravagant situation

6 None of the Reorganization Plans so far submitted by the President will result in economy but all will effect a concentration of political power and prestige

Respectfully submitted
By direction of the President
CHARLES G HAYDEN, M D, Chairman
Subcommittee of National Legislation

APPENDIX NO 7

REPORT OF THE COMMITTEE ON ARRANGEMENTS

The Committee on Arrangements wishes to report that the dates of May 15, 16, 17 and 18, 1950, have been selected for the 1950 annual meeting of the Society, and that the next annual meeting of the Council will be held on the evening of May 15 in Boston

It is recommended that these dates be approved by the Council

GORDON DONALDSON, M D
ALBERT EHRENFRIED, M D
JAMES A HALSTED, M D
JOHN W NORCROSS, M D
FRANKLIN G BALCH, JR, M D, Chairman

APPENDIX NO 8

REPORT OF THE COMMITTEE ON PUBLIC HEALTH

On August 10, 1949, a meeting of the Committee was held at the Hotel Kenmore, Boston, to discuss the relation of the Massachusetts Medical Society to the increased incidence of poliomyelitis. Present at this meeting were the following: Arthur W. Allen, M.D., H. Quimby Gallup, M.D., Joseph Garland, M.D., Charles Bradford, M.D., Vlado A. Getting, M.D., Roy Feemster, M.D., Roy J. Ward, M.D., Alfred L. Frechette, M.D., Warren R. Sisson, M.D., and John J. Poutas, M.D.

The first item of business was the election of a secretary for the Committee. John J. Poutas, M.D., was re-elected secretary for the fourth consecutive year.

Next on the agenda was consideration and approval of proposed minimal "Standing Orders" for use in convalescent and nursing homes. This material was submitted to the committee by Dr. Alton S. Pope, deputy commissioner of Health, and was discussed at this meeting by Dr. Getting, commissioner of health. The purpose of the standing orders is to restrict self-medication to a minimum. The proposed standing orders were read by the secretary, and it was pointed out that they are "minimals." It was moved and voted that they be approved in principle.

A letter, written by Francis C. Hall, M.D., president, New England Chapter, Arthritis and Rheumatism Foundation, to Dr. Arthur W. Allen, was read in which the assistance of the Society was requested in a survey to ascertain the number of arthritis clinics in the State and to render advice regarding encouragement and expansion of any existing clinics and the wisdom of establishing new clinics.

The Committee voted approval of this survey and recommended that it be accomplished with and through the office of the Commissioner.

A request by the same foundation that an arthritis subcommittee of the Committee on Public Health be appointed was approved and it is accordingly referred to the Council for necessary action.

The main item of business on the agenda consisted of a detailed discussion of the situation in the State and country with respect to infantile paralysis.* Drs. Getting and Feemster gave a very detailed outline of the problem and presented the following for committee action:

A proposed newspaper release to the effect that the Committee on Public Health and the Massachusetts Department of Public Health had jointly considered and approved a set of recommended practices for the control of poliomyelitis adopted by a national conference in Ann Arbor, Michigan, in June, 1949, under the auspices of the National Foundation for Infantile Paralysis. The Committee considered in detail the proposed release, and approval was duly voted.

It was also proposed and voted that these recommended practices be given the earliest possible publication in the *New England Journal of Medicine* and disseminated to all physicians.

The advisability of radio broadcasts by a panel of physicians on the general subject of infantile paralysis was discussed, moved and voted.

The Committee then formally offered its commendation to Dr. Getting for the excellence of his department and the splendid and effective co-operation it has always shown to this committee.

ALFRED L. FRECHETTE, M.D.
JOHN J. POUTAS, M.D.
WARREN R. SISSON, M.D.
CONRAD WESSELHOEFF, M.D.
ROY J. WARD, M.D. *Chairman*

*Two additions to the report were made by the Council by recommendation of the Committee—namely, approval of the survey of multiple sclerosis by the Harvard School of Public Health and approval of the Chest X-Ray Program in Boston.

APPENDIX NO 9

REPORT OF THE COMMITTEE ON MEMBERSHIP

A regular meeting of the Committee on Membership was held on August 10, 1949. The Committee discussed the question of the possibility of amending the by-laws relating to applicants for membership in the Society with particular reference to Chapter 5, Section 2b which states that "applica-

tions from a graduate of a discontinued medical school or a foreign medical school may apply only when the applicant has possessed a license to practice medicine in the United States or its territories for at least five years."

It was felt that the original reason for this by-law was largely past since the last unapproved medical school had now been closed.

It was felt further that there would be a few cases in which an unjust hardship would be placed upon some well intentioned graduate of an unapproved school if he was not allowed to have the privilege of membership in the Society during the first five years of his practice.

Therefore, it was voted that it be recommended that the following change be made in paragraph 2 of Section 2(b) of Chapter V: "The applicant has possessed a license to practice medicine in the Commonwealth and has conducted that practice in the district from which he makes application, for at least one year."

The following reasons for this change are given: knowledge of the doctor by his fellows for one year is better than registration for any length of time elsewhere, the Committee on Membership has often turned down otherwise eligible candidates because they were not known in the town or city for at least a year, the first five years of practice are the hardest, and the by-laws make them more difficult because the doctor cannot become a staff member in an approved hospital until he is a fellow of the Society and he cannot, therefore, take advantage of the Gallup Plan because most hospitals stick to the ruling mentioned above, if this by-law were changed, more hospitals would accept the Gallup Plan, the applicant would be able to give better care to his patients, this is the ultimate objective of the Society, it would be a good public-relations effort, and the number of such applicants is steadily decreasing.

The vote was four in favor of this recommendation and one opposed (by proxy).

WILLIAM A. R. CHAPIN, M.D.
HENRY F. HOWE, M.D.
DONALD MUNRO, M.D.
SAMUEL N. ROSE, M.D.
LEWIS S. PILCHER, M.D. *Chairman*

APPENDIX NO 10

REPORT OF THE COMMITTEE ON SOCIETY HEADQUARTERS

It is the opinion of the Committee that a survey to see what is the best thing to do for the future home of the Society should be made, and that the present headquarters, the present facilities, and the possibility of obtaining more land and buildings in the near neighborhood, such as the Bostonian Hotel and the tenements on Hemingway Street across from the Library should be examined, the possibility of acquiring land at the dam site where the Boston Museum of Natural History is contemplating building should be investigated and that it should be known whether or not it might be advisable to obtain a piece of land and combine, on this land, the Medical Library, the *Journal* office, the headquarters, and a building for the Massachusetts Medical Society in co-operation with the School of Public Health of Harvard, which is moving to build a new building, and combining, at the same time, with the Department of Public Health. It is recommended that the Society employ a man to survey all the possibilities and make a final report to the Council. It is also recommended that a sum, not exceeding \$5000, be appropriated to carry out the thorough survey that is recommended.

JOSEPH S. BARR, M.D.
ALBERT A. HORNOR, M.D.
DWIGHT O'HARA, M.D.
WALTER G. PHIPPEN, M.D.
FRANK R. OBER, M.D. *Chairman*

APPENDIX NO 11

REPORT OF THE COMMITTEE ON INDUSTRIAL HEALTH

The Committee met at the Harvard Club on July 20, 1949, to outline a program for the coming year. Besides the members of the committee, Dr. William Fleming, of Boston University, Dr. Dwight O'Hara, of Tufts, Dr. Albert Seeler, of Harvard School of Public Health, the members of the Advisory Committee and the officers of the Society were present.

The following suggestions were made concerning the program a survey should be made of the industrial-health facilities in the State, the need for instruction in industrial health in medical schools, in postgraduate courses and in industrial plants, the need for a series of programs for professional and lay people concerning industrial-health problems, the need for a clearing house of industrial-health information, and the need for insurance covering the worker for industrial and nonindustrial disabilities.

The Committee recommends that an industrial-health conference be held in Boston on December 14, 1949, under the auspices of the Society. The program will consist of a morning session devoted to industrial medicine and surgery, an afternoon session for management, labor, state agencies and insurance companies, and an evening session of general interest to all.

If this recommendation is approved, the conference program will be directed by Dr George Wilkins, Dr Karl Benedict and Dr John Poutas.

The survey of industrial-health facilities will be conducted by Dr George Morris, Dr Harriet Hardy and Mr William Seymour.

KARL T BENEDICT, M D
HARRIET L HARDY, M D
DANIEL L LYNCH, M D
GEORGE E MORRIS, M D
JOHN J POUTAS, M D
GEORGE F WILKINS, M D
HENRY C MARBLE, M D, *Chairman*

APPENDIX NO 12

REPORT OF THE COMMITTEE TO MEET WITH THE MASSACHUSETTS HOSPITAL ASSOCIATION

Since the request from Norfolk District Medical Society to the Council "for a delineation of the developments which had taken place regarding the report of the Committee on Special Services" and the resolution from the joint Committee of the Anesthesiologists, Pathologists, Physical Therapists, and Roentgenologists that "the Committee from the Massachusetts Medical Society to meet with the Massachusetts Hospital Association be instructed to take steps to expedite the acceptance and practice of the principles enunciated by the Committee to study Special Services" are so similar as to be practically concomitant they will be answered together.

First we wish to quote from the report made to the Council on May 24, 1948, by this committee of the previous conference held March 3, 1948, with the Committee on Professional Services of the Massachusetts Hospital Association when we tried to get their approval of the principles enunciated by the Committee to Study Special Services. The Society was represented by Drs Bagg and Gallupe and four members of the Committee, which included Dr McKittrick. The Hospital Association was represented by Dr Norbert A Wilhelm, of the Peter Bent Brigham Hospital, and Mr Warren F Cook, of the New England Deaconess Hospital.

Arguments about why these principles should be approved by the Hospital Association were presented, chiefly by Drs Bagg and McKittrick. Dr Wilhelm stated that his committee had met the day previously and had voted that no action be taken at this time. Their decision was based chiefly upon their belief of the uncertainty whether the Blue Cross could continue to provide adequate prepaid hospital insurance. As hospital administrators they believed its successful operation was essential to the welfare of hospitals, and they refused to approve anything they thought might further embarrass it. They also said that because of poor public relations on the part of the hospitals, a more complicated system of billing hospital costs to the patient would be too confusing and undesirable to be undertaken. Incidentally, they stated they believed that very few hospitals had a system of accounting sufficiently comprehensive to be able to work out all details of cost accounting that would be necessary under this plan.

There was a great deal of discussion during which the representatives of the Society tried unsuccessfully to convert the representatives of the Association to its point

of view. They were unwilling to grant their approval of these principles even though the Society agreed to the postponement of their adoption until a later date because they believed that in these days when the Blue Cross and so many hospitals are in great financial distress, the whole question of voluntary hospital service is at stake. They insisted that now was not the time to undertake the adoption of these principles. Although the Committee believed in the fairness of these principles and urged their adoption, it was believed that the representatives of the Association were sincere in their point of view. As a result of this conference, it was believed that nothing more could be done at present.

From this quotation it is obvious that the statement contained in the preamble to the resolution presented by the Joint Committee of the Anesthesiologists, Pathologists, Physical Therapists, and Roentgenologists that "it was decided not to press for acceptance and practice of the principles enunciated by the Committee to Study Special Services at that time, etc." does not represent the intentions, the sincerity, or the efforts of the Committee at that meeting. There was plenty of explanation, persuasion, and pressure on the part of the Committee but they, particularly Dr Wilhelm, were steadfast in refusing to agree to anything for the reasons given.

Late last fall the Chairman, mindful of the Council vote that this committee continue its efforts, consulted the secretary of the New England Pathological Society (Dr Nickerson), who was a member of the original Committee to Study Special Services as to whether or not they wished us again to communicate with the Committee on Professional Services of the Massachusetts Hospital Association for more discussion of the McKittrick Report. He was told that they did not at that time, since the general situation was unchanged. He stated that with Dr McKittrick on both the Blue Shield and Blue Cross boards, he felt the interests of the special services would be safeguarded. He also said they might again bring up their problem at a later time. That request was made at the Council Meeting on the evening of May 23 in a resolution representing a Joint Committee of the Anesthesiologists, Pathologists, Physical Therapists, and Roentgenologists requesting this committee "to take steps to expedite the acceptance and practice by the Massachusetts Hospital Association of the principles enunciated by the Committee to Study Special Services."

The second and most recent meeting with the Professional Services Committee of the Massachusetts Hospital Association was held June 30, 1949. This time each side was represented by a new committee. On that for Professional Services of the Hospital Association were Dr Guy W Brugler, director of the Children's Hospital, Mr Warren F Cook, executive director of the New England Deaconess Hospital, and Mr Paul F Nallon, superintendent of the Hampden County Hospital in Greenfield.

The Committee representing the Society now has an anesthesiologist, a pathologist and a roentgenologist.

Present at this meeting were the members of the Committee and Dr Leland S McKittrick, president-elect of the Society. Dr Arthur W Allen, president of the Society, attended a conference held prior to the meeting with the Hospital Association and joined in a discussion of the problem. Dr Brugler and Mr Nallon appeared for the Hospital Association. Mr Cook sent word that he was unable to attend although we did not know it until the conference began. Also, the date for the meeting had been arranged through his office before the notices were sent out.

Beginning with Dr Donald A. Nickerson, pathologist at the Salem Hospital, where the principles in the McKittrick Report were accepted and put in practice a year ago, the Committee did the best it could by explanation, argument and persuasion to convince the two members of the Professional Services Committee that the Massachusetts Medical Society really supports these principles enunciated by the Committee to Study Special Services. Dr McKittrick spoke at length in favor of these principles and reported that the Massachusetts General Hospital is now reorganizing its departments to conform to them. Their attention was also called to the fact that the Committee on Hospitals and Practice of Medicine of the American Medical Association had included these principles in their report to the

House of Delegates, which was accepted, and gave a strong endorsement urging that they be approved and adopted generally.

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(11) Physicians and other qualified persons rendering medical care shall receive adequate remuneration for their services.

(12) The physician shall be free to elect or reject without prejudice participation in a medical-care plan. The

rights of the physician as to the choice of methods by which he is to be paid shall be fully protected.

(13) We agree that the federal Government may properly assist financially such medical schools as are found unable to meet their operative costs, upon their request for such assistance, *provided* that such assistance shall not be construed as authorizing any federal department, agency, officer or employee to exercise any supervision or control over the admission of students, curriculum, teaching personnel or administration of such medical schools, except such supervision as may be necessary to ensure that grants shall be expended solely for the purpose for which they are made.

(We believe effective organizations of state and district health councils would immeasurably improve the community concept of local health needs. The initiative of the people themselves, and especially of the medical and public health personnel, must provide the spark.)

(14) The Massachusetts Medical Society looks upon these basic principles as essential to the development of any successful medical-care plan and, as guides by which to evaluate medical-care plans that may be proposed in the future, with the understanding that changing conditions may require their later revision.

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This is an innovation for the New England Assembly, and it is hoped that with careful attention to details it will become a very valuable adjunct to the meeting. It was initiated by Mr. Boyd when in discussion it was felt that the clinics at the various hospitals provided a very uncertain attendance.

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APPENDIX NO 18

REPORT OF THE COMMITTEE TO WRITE A PUBLICITY CODE

In accordance with the vote of the Council at their meeting on May 23, 1949, at which time it was moved and voted that "a committee of five write a Massachusetts Medical Society code to govern publicity," the following report and recommendations are submitted

A It is recommended that the following Publicity Code of the Massachusetts Medical Society be accepted

Publicity Code
of the
Massachusetts Medical Society

PREAMBLE Believing that the relationship between organized medicine as represented in this Commonwealth by the Massachusetts Medical Society and the public as represented by the press, the radio, non-medical magazines and other similar media of communication should be cordial, co-operative and more closely integrated than it has been in the past, the Council of the Massachusetts Medical Society acting for the Society in a regular meeting hereby authorizes the following Publicity Code to implement such relationship

1 This document shall be known as the Publicity Code of the Massachusetts Medical Society

2 The purpose of this code is to establish acceptable ethical limits within which Fellows of the Society who are also members of hospital staffs or of administrative departments of hospitals or other institutions devoted exclusively to the teaching, investigation or practice of medicine may contribute in writing or by interview to the non-medical press and magazines or the radio or other media of communication

3 This code shall be supplemental to the present codes of ethics that govern the Fellows of the Massachusetts Medical Society

4 The name of any Fellow of the Massachusetts Medical Society as designated in Section 2 of this code may be used for purposes of publicity only with permission of the Chief of Staff or the Chief of the appropriate service of the hospital and of the hospital director. This permission applies only provided that the Fellow is identified as a member of the staff rather than as an individual and where the emphasis is on the services rendered and not on the individual Fellow

5 If the hospital organization does not include a Chief of Staff or Chief of Service, the name of any Fellow may be used for purposes of publicity as otherwise limited in Sections 2 and 4 of this code only after permission has been obtained from the Supervising Censor of the District Society of which the Fellow in question is a member. Permission from the hospital director will not suffice in these circumstances

6 In the case of institutions other than hospitals devoted exclusively to the teaching, investigation and practice of medicine, the name of any Fellow may be used for purposes of publicity only as follows: A With permission of the head of a major department or research organization. B With permission of the Dean of a Medical School or someone specifically designated by him for this purpose. These permissions apply only if the emphasis is placed on the services rendered or work done rather than on the individual Fellow

7 The name of any Fellow may be used in connection with an individual case or project with the consent of the individual Fellow and in accordance with the requirements listed in Sections 4, 5 and 6 of this code. This permission applies only whenever the case or project illustrates the work performed at the hospital or the institution (see Sections 4, 5 and 6 of this code) and the emphasis is placed on the services rendered or work done and not on the individual Fellow

8 The name of any Fellow may be used in information given out about a patient or a project in conformity with the requirements listed above in Sections 4, 5 and 6 of this code whenever the press, magazines, radio and other media of communication have most of the facts already and are calling the hospital or institution for purposes of verification of data received from other sources

9 Fellows of the Massachusetts Medical Society as described in Section 2 of this code who are contacted directly by representatives of the press, magazines, radio or other media of communication and who are unwilling to conform to the requirements as laid down in Sections 4, 5, 6, 7 and 8 of this code must consider themselves responsible for the contents of said interviews regardless of their alleged accuracy or inaccuracy

10 Except as specified in Section 9 of this code Fellows of the Massachusetts Medical Society as described in Section 2 of this code, the use of whose name by the press, magazines, radio or other media of communication has not been specifically authorized in accordance with the provisions of Sections 4, 5, 6, 7 and 8 of this code shall after investigation by the proper authorities be held absolved of all blame for such authorized use regardless of the accuracy or inaccuracy of the article or interview in question

11 It is recommended that Fellows of the Massachusetts Medical Society who are forced to respond to inquiries from the press, magazines, radio or other media of communication without an opportunity to invoke the provisions listed in Sections 4, 5, 6, 7 and 8 of this code limit their reply to the single statement, "No Comment."

12 Violations of this Publicity Code by Fellows of the Massachusetts Medical Society shall be subject to review by the Committee on Ethics and Discipline of the Massachusetts Medical Society. The Committee on Ethics and Discipline may initiate action for this purpose or may take action in response to written complaints relative to infractions of this code provided the complaint is signed by the complainant. The decisions of the Committee on Ethics and Discipline shall be rendered in accordance with Chapter VII, Section 9 of the By-Laws of the Massachusetts Medical Society

B Your committee is strongly of the opinion that the scope of this code should be widened and its influence extended. To accomplish these ends it is desirable that governing Boards of Hospitals, hospital directors, authoritative representatives of the press, of the non-medical magazines, of the radio and of other similar media of public communication be informed of this desire as coming from the Massachusetts Medical Society as well as the Society's willingness to co-operate with these agencies to that end

Your committee therefore recommends that it be continued in existence for this purpose

C Your Committee further recommends that this code be included with the By-Laws and Code of Ethics presently in preparation for publication and distribution to the Fellows of the Massachusetts Medical Society

RALPH R. STRATTON, M.D.

JOHN F. CONLY, M.D.

CHARLES C. LUND, M.D.

LEROY A. SCHALL, M.D.

DONALD MUNRO, M.D., Chairman

APPENDIX NO 19

REPORT OF THE MEETING OF THE HOUSE OF DELEGATES OF AMERICAN MEDICAL ASSOCIATION

The attendance at the meeting of the American Medical Association in Atlantic City was the second largest of the 87 previous sessions. The technical and scientific exhibits were crowded all the time and the color television of actual operations performed by nationally known surgeons at the nearby Atlantic City Hospital evoked unusual interest.

The House of Delegates met on the morning of the 6th at the Travmore Hotel and continued in session until the 9th. There was the usual high percentage of attendance and considerable business was accomplished. Your delegates were all present and were given the following reference committee appointments

Dr. Alchittreck — chairman Emergency Medical Service
Dr. Phippen — member — Legislation and Public Relations
Dr. Rickham — member — Reports of Officers
Dr. Curley — Corps of Sergeant-at-Arms

Dr. Phippen also served on the committee to nominate candidates for the Distinguished Service Award and on the

rights of the physician as to the choice of methods by which he is to be paid shall be fully protected

(13) We agree that the federal Government may properly assist financially such medical schools as are found unable to meet their operative costs, upon their request for such assistance, *provided* that such assistance shall not be construed as authorizing any federal department, agency, officer or employee to exercise any supervision or control over the admission of students, curriculum, teaching personnel or administration of such medical schools, except such supervision as may be necessary to ensure that grants shall be expended solely for the purpose for which they are made

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In further considering the method of collection, two points are important that the Red Cross method of voluntary free donation is still new and in a trial period that will probably have to go on for months or even several years before we can logically determine whether it will be a success or failure, and to be successful, it must have the full active support of the medical profession, any action short of which might cripple the program, which would be unfortunate as well as rendering us somewhat lame. We discussed a number of minor difficulties with the program, most of which we felt could be ironed out at the Red Cross advisory meetings, since any public recommendations made to correct them might contribute to shaking public confidence in the program as a whole. The essential difficulty of the Red Cross Program is an insufficient number of donors. When it can collect enough blood, most present problems will solve themselves.

The Committee recommends that the Society give both verbal and active assistance to ensure the success of the Red Cross State Blood Program, because its success will be a great boon to patients and to physicians alike.

It further recommends the following specific measures to assist the program:

That the editorial board of the *Journal* should from time to time write editorials expressing approval of the Red Cross program and explaining the purpose, its value to patients and to doctors and explaining what doctors can do locally to help—it should stress the following points: the value of blood and blood derivatives without payment for the product, the fact that hospitals and doctors will not lose money by banding this blood, since reasonable charges for laboratory work administration will continue as before, that local blood banks will be encouraged to exist and will probably flourish under this system, that the establishment of local storage depots by the Red Cross at strategic sites in the State has already begun and will probably be expanded that the supplying of blood by the Red Cross to the small hospitals where the use of blood is sporadic but vital has already been of great value and will be expanded, that all doctors should realize the value of the program to themselves and should take an active part in their local Red Cross program to ensure that collections be at a high level and distribution on the best possible basis for their needs, the whole success of the program resting on large collections (this they can do by joining the blood program committee of their local chapters, setting an example in their communities by their own, or family donation of blood to the Red Cross, serving as speakers for their Red Cross chapters, discussing with their local chapters, or the directors of the program, any problems that arise in their use of blood, informing their patients or their families when they have received blood or albumin or gamma globulin from the Red Cross and encouraging them to replace it, and setting up in co-operation with the Red Cross a program for distribution from one hospital to another in case of need).

That the Red Cross should expedite its collection of blood in the metropolitan area by establishment of a donor center in Boston.

That the Committee be authorized to write to hospitals and district medical societies to find out how the blood program is working locally and on the basis of its findings make recommendations to the Red Cross through the Red Cross Advisory Committee, several members of which serve on this committee.

That the Red Cross should extend its advertising and publicity campaigns to obtain a better response from the public.

That one of the really great problems in this state at present is the inadequate technical training of many of the persons responsible for grouping and cross matching—a problem beyond the scope of the activities of the Red Cross, but one that this committee should solve a sub-committee made up of Dr William Moloney and Dr F. H. Allen investigated the matter and on the basis of their studies this committee submits the following recommendations for the improvement of the situation that it should be brought to the attention of district medical societies and hospital directors by the Executive Committee of the Massachusetts Medical Society that the correct grouping and cross-matching of patients before

transfusion remains the legal responsibility of the doctor administering the blood and of the hospital in which the transfusion is given, that in some instances this is now being done by ill trained personnel, which can cause serious mistakes (according to a survey made by Dr McReady of the State Biological Laboratory there are a number of hospitals in which the grouping and cross-matching are done by untrained persons), that this can be remedied by training the persons conducting the grouping and cross-matching, that this training can be carried out at the State Blood Grouping Laboratory free of charge, and by the larger blood banks—the members of this committee who represent blood banks have expressed their willingness to do this—when the Red Cross blood laboratory is opened it will be able to participate in a training program and that current work on new and better techniques is so encouraging that we should wait another three to six months for their development before initiating such a training program.

F. HAROLD ALLEN, JR., M.D.

STEPHEN BROWN, M.D.

CHARLES EMERSON, M.D.

HAROLD B. KENTON

WILLIAM C. MOLONEY, M.D.

JOSEPH F. ROSS, M.D.

LAMAR SOUTTER, M.D., *Chairman*

APPENDIX NO 21

REPORT OF THE COMMITTEE ON BLUE CROSS-BLUE SHIELD PROBLEMS

A meeting of the Committee was held on July 29, 1949, at 8 Fenway. The Blue Shield program of payments for the care of ward cases in teaching hospitals was discussed. Representatives of the Massachusetts General Hospital, Children's Hospital and Massachusetts Eye and Ear Infirmary, Boston Floating Hospital and Blue Shield were present. The hospitals had been informed that payments had not been made to doctors caring for Blue Shield patients on the wards. The hospitals had replied that it was not the policy in their institution to consider ward patients as private patients and to place them in that category would injure the teaching program.

Blue Shield suggested that staff doctors form groups to receive Blue Shield fees and to disburse the money as they saw fit.* One hospital representative stated that the group in his hospital had employed the money collected for laboratory research, intern travel expenses, postgraduate education and so forth.

It was the opinion of the Committee that teaching facilities in these hospitals must be maintained, and that Blue Shield fees for the care of these patients when requested by a particular hospital staff be paid to doctors or a group of doctors and not to a hospital, and that when paid the monies may be used for any purposes decided by a vote of the doctors concerned.

The House of Delegates of the American Medical Association meeting at Atlantic City in June 1949, dissolved all formal relations existing between the American Medical Association and Associated Medical Care Plans, the national association of Blue Shield plans. In effect this action means that the Council on Medical Service of the American Medical Association will no longer be represented on the Blue Shield Commission, which is the governing board of A.M.C.P., and that the implied objection of the American Medical Association to the formation of a Blue Shield insurance company better to serve national accounts has been removed.

The Blue Shield Commission has already taken preliminary steps to establish a national insurance company and is only awaiting approval by a majority of plans before bringing

*The Council amended this report by deleting the lines beginning with the word "The" in the third sentence of the first paragraph and ending with the word "fit" in the second paragraph and substituting the following: "It was pointed out that until about a year ago Blue Shield made no payments for medical services rendered to ward service cases because it was the confirmed policy of the hospitals involved that staff physicians should not bill for such services. During 1948 this policy on the part of several teaching hospitals was altered to the extent that staff groups but not individual physicians were permitted to receive payments from third parties such as Blue Shield and commercial insurance companies for medical services rendered to service ward patients. Formal group arrangements were made at two hospitals and informal group arrangements were made at several other hospitals after which Blue Shield began making payment to these groups."

so-called Hess Committee on Practice of Medicine by Hospitals

The Distinguished Service Award was given to Dr Seal Harris, of Alabama, by vote of the House of Delegates

The highlight of the first morning session was the announcement by the chairman of the Board of Trustees of the curtailment of Dr Fishbein's activities. This is old news now, but as a matter of fact it did not occasion quite the stir that the newspapers would have you to believe. Nearly everyone expected something of the kind would happen. Every member of the House appreciates Dr Fishbein's ability and capacity for work and realizes what he has accomplished with the *Journal*. I think most of them felt very sorry but realized that it was a move in the best interests of all the members of the American Medical Association. He will actually retire when the reorganization of the editorial office has been accomplished and his successors trained for the jobs. (I believe there will be four)

The Committee on Emergency Medical Service reported that the status of the Surgeon General of the Army had been much improved. He now has supreme authority in the Army Medical Department reporting directly to the Chief of Staff and not through the Adjutant General's office as heretofore. It also announced the establishment of a Division of Medical Service in the office of the Secretary of Defense and that the first Director of Medical Services of the armed services had been appointed. This should bring about more co-operation between the Medical Corps of the Army, Navy and Air.

The House approved a resolution from the Section of Anesthesiology recommending the trustees to provide funds for a study of operating-room deaths.

The House adopted the recommendation of the Council on Medical Service as follows:

The formation of a national co-ordinating agency representing all qualified voluntary prepayment plans in accordance with the proposal made to the Board of Trustees by the Council on Medical Service, that there shall be no official connection between the American Medical Association and the Associated Medical Care Plans, however, the American Medical Association will continue to approve or disapprove all voluntary medical-care plans, the recognition of A M C P as a trade organization of member plans and Blue Cross as occupying a similar position for voluntary prepayment hospital care plans, the recognition of the responsibility of the American Medical Association to promote the principle of voluntary insurance by educating the people as to their need for such coverage and by obtaining full co-operation from state and county medical organizations in the local field and to inform the American people of the availability of approved plans that propose to supply on a prepayment basis security against the economic hazards of serious illness.

The House approved a report of the Council of Medical Service setting forth 20 principles as guides for approving lay-operated medical-care plans. This is a progressive step since there are already 171 lay-operated or consumer-sponsored plans in 43 states. There are now 95 sponsored by medical societies.

The House approved sponsorship of a national health conference to encourage discussion of the American Medical Association twelve-point program by farm, labor and other lay organizations.

A resolution was introduced aimed to limit the care of non-service-connected disability by the Veterans Administration, and to limit the hospital-building program of the Veterans Administration. This was reported favorably by the reference committee but was rejected by the House. It was later reconsidered and after considerable discussion was referred to the Board of Trustees for further consideration.

The House adopted a resolution creating a special committee composed of members of the Board of Trustees, House of Delegates and other fellows of the Association to arrange a conference with members of Congress with a view of developing legislation that would meet the objectives of the American Medical Association program in its effort to solve the problem of making medical care more readily accessible to the American people. This committee would work in co-operation with other existing committees and make its report from time to time to the Board of Trustees.

The Committee on Hospitals and the Practice of Medicine defined the corporate practice of medicine and gave a summary of the laws covering the practice of medicine in all states. It reiterated the fact that neither hospital nor doctor should be exploited at the expense of the other. It urged that all specialists should be regularly appointed members of the medical staff with a voice in its management. It concluded that most controversies should be settled at the local level and suggested that every component society appoint a committee on hospitals and professional relations.

The reference committee in recommending the adoption of this report further reminded the delegates that the Judicial Council had jurisdiction in such matters and might, if the evidence warranted, find either the hospital or lay group guilty of violating the Principles of Ethics and recommend that the Judicial Council withdraw the Association's approval of a hospital that did not comply.

The House approved the following resolution that the House of Delegates of the American Medical Association express its disapproval of the extension of so-called "social security" to self-employed persons, including physicians and surgeons. This resolution has now been mailed to all state secretaries, urging them to interest their members in opposing this legislation.

Much other business was transacted, and the House accomplished a good deal of work in a short time.

WALTER G. PHIPPEN, M.D.

APPENDIX NO 20

REPORT OF THE ADVISORY COMMITTEE FOR RED CROSS BLOOD BANK

On July 20, 1949, the Committee met to consider various problems in connection with blood collection and distribution. The entire committee was present except for Dr. Joseph Ross, who was unable to attend. Because we felt that the success of our work would depend on a very close relation with the Red Cross, and that no help that we might be able to give the Red Cross would be valuable unless they both understood and desired it, we invited Dr. William Freeman, of Fall River, the state medical director of the Red Cross program, to attend. He came to the meeting and gave us a considerable amount of help.

It was the feeling of the Committee that we should first decide whether we considered the Red Cross program to be valuable to both patients and the medical profession of the State. We discussed this matter at some length and came to the conclusion that it was indeed valuable. We have all served in an advisory capacity to the Red Cross—Dr. Brown in Northampton, and the rest of us in the metropolitan area. We have therefore been cognizant of the fact that the present program of blood collection and distribution was more or less forced upon the Red Cross in March, 1948, when funds were no longer forthcoming from the State for the maintenance of the blood program. This has meant, of course, that the support of the medical profession has been vital for the Red Cross to carry on with the program, which, although still in its infancy and small, was already valuable.

The fundamental purpose behind the National Red Cross Blood Program has been twofold—namely, the setting up of a program, which, in the event of local or nation-wide catastrophe, would be able to supply blood throughout the country, and, at the same time, to make blood available to all who need it in hospitals everywhere without charge for the product. Whether or not the Red Cross is the logical agency for setting up a nation-wide program we did not feel to be a matter for our consideration, since such a program has already been set up at the instigation of and with the sanction of the federal Government.

Blood for all, without the necessity for establishing credit or making repayment, is extremely worthy on an idealistic basis. All of us, however, have had considerable experience with the collection of blood in our own hospitals. Some of us are not thoroughly convinced that a sufficiently high level of public enthusiasm can be permanently maintained in the absence of a national catastrophe to ensure a steady supply of the amount of blood necessary to meet hospital needs.

In further considering the method of collection, two points are important that the Red Cross method of voluntary free donation is still new and in a trial period that will probably have to go on for months or even several years before we can logically determine whether it will be a success or failure, and to be successful, it must have the full active support of the medical profession, any action short of which might cripple the program, which would be unfortunate, as well as rendering us somewhat to blame. We discussed a number of minor difficulties with the program, most of which we felt could be ironed out at the Red Cross advisory meetings, since any public recommendations made to correct them might contribute to shaking public confidence in the program as a whole. The essential difficulty of the Red Cross Program is an insufficient number of donors. When it can collect enough blood, most present problems will solve themselves.

The Committee recommends that the Society give both verbal and active assistance to ensure the success of the Red Cross State Blood Program, because its success will be a great boon to patients and to physicians alike.

It further recommends the following specific measures to assist the program

That the editorial board of the *Journal* should from time to time write editorials expressing approval of the Red Cross program and explaining the purpose, its value to patients and to doctors, and explaining what doctors can do locally to help—it should stress the following points: the value of blood and blood derivatives without payment for the product, the fact that hospitals and doctors will not lose money by handling this blood, since reasonable charges for laboratory work administration will continue as before that local blood banks will be encouraged to exist and will probably flourish under this system that the establishment of local storage depots by the Red Cross at strategic sites in the State has already begun and will probably be expanded that the supplying of blood by the Red Cross to the small hospitals where the use of blood is sporadic but vital has already been of great value and will be expanded, that all doctors should realize the value of the program to themselves and should take an active part in their local Red Cross program to ensure that collections be at a high level and distribution on the best possible basis for their needs, the whole success of the program resting on large collections (this they can do by joining the blood program committee of their local chapters, setting an example in their communities by their own, or family donation of blood to the Red Cross, serving as speakers for their Red Cross chapters, discussing with their local chapters or the directors of the program, any problems that arise in their use of blood informing their patients or their families when they have received blood or albumin or gamma globulin from the Red Cross and encouraging them to replace it, and setting up in co-operation with the Red Cross a program for distribution from one hospital to another in case of need).

That the Red Cross should expedite its collection of blood in the metropolitan area by establishment of a donor center in Boston.

That the Committee be authorized to write to hospitals and district medical societies to find out how the blood program is working locally and on the basis of its findings make recommendations to the Red Cross through the Red Cross Advisory Committee, several members of which serve on this committee.

That the Red Cross should extend its advertising and publicity campaigns to obtain a better response from the public.

That one of the really great problems in this state at present is the inadequate technical training of many of the persons responsible for grouping and cross matching—a problem beyond the scope of the activities of the Red Cross, but one that this committee should solve a sub-committee made up of Dr William Moloney and Dr F. H. Allen investigated the matter and on the basis of their studies this committee submits the following recommendations for the improvement of the situation that it should be brought to the attention of district medical societies and hospital directors by the Executive Committee of the Massachusetts Medical Society that the correct grouping and cross-matching of patients before

transfusion remains the legal responsibility of the doctor administering the blood and of the hospital in which the transfusion is given, that in some instances this is now being done by ill trained personnel, which can cause serious mistakes (according to a survey made by Dr McReady of the State Biological Laboratory there are a number of hospitals in which the grouping and cross-matching are done by untrained persons), that this can be remedied by training the persons conducting the grouping and cross-matching, that this training can be carried out at the State Blood Grouping Laboratory free of charge, and by the larger blood banks—the members of this committee who represent blood banks have expressed their willingness to do this—when the Red Cross blood laboratory is opened it will be able to participate in a training program and that current work on new and better technics is so encouraging that we should wait another three to six months for their development before initiating such a training program.

F. HAROLD ALLEN, JR., M.D.

STEPHEN BROWN, M.D.

CHARLES EMERSON, M.D.

HAROLD B. KENTON

WILLIAM C. MOLOVEY, M.D.

JOSEPH F. ROSS, M.D.

LAMAR SOUTTER, M.D., *Chairman*

APPENDIX NO 21

REPORT OF THE COMMITTEE ON BLUE CROSS-BLUE SHIELD PROBLEMS

A meeting of the Committee was held on July 29, 1949, at 8 Fenway. The Blue Shield program of payments for the care of ward cases in teaching hospitals was discussed. Representatives of the Massachusetts General Hospital, Childrens' Hospital and Massachusetts Eye and Ear Infirmary, Boston Floating Hospital and Blue Shield were present. The hospitals had been informed that payments had not been made to doctors caring for Blue Shield patients on the wards. The hospitals had replied that it was not the policy in their institution to consider ward patients as private patients and to place them in that category would injure the teaching program.

Blue Shield suggested that staff doctors form groups to receive Blue Shield fees and to disburse the money as they saw fit.* One hospital representative stated that the group in his hospital had employed the money collected for laboratory research, intern travel expenses, postgraduate education and so forth.

It was the opinion of the Committee that teaching facilities in these hospitals must be maintained, and that Blue Shield fees for the care of these patients when requested by a particular hospital staff be paid to doctors or a group of doctors and not to a hospital, and that when paid the monies may be used for any purposes decided by a vote of the doctors concerned.

The House of Delegates of the American Medical Association meeting at Atlantic City in June, 1949, dissolved all formal relations existing between the American Medical Association and Associated Medical Care Plans, the national association of Blue Shield plans. In effect this action means that the Council on Medical Service of the American Medical Association will no longer be represented on the Blue Shield Commission, which is the governing board of A M C P, and that the implied objection of the American Medical Association to the formation of a Blue Shield insurance company better to serve national accounts has been removed.

The Blue Shield Commission has already taken preliminary steps to establish a national insurance company and is only awaiting approval by a majority of plans before bringing

*The Council amended this report by deleting the lines beginning with the word "The" in the third sentence of the first paragraph and ending with the word "fit" in the second paragraph and substituting the following: "It was pointed out that until about a year ago Blue Shield made no payments for medical services rendered to ward service cases because it was the confirmed policy of the hospitals involved that staff physicians should not bill for such services. During 1948 this policy on the part of several teaching hospitals was altered to the extent that staff groups, but not individual physicians, were permitted to receive payments from third parties, such as Blue Shield and commercial insurance companies for medical services rendered to service ward patients. Formal group arrangements were made at two hospitals and informal group arrangements were made at several other hospitals after which Blue Shield began making payment to these groups."

the matter to a conclusion. The Board of Directors of Massachusetts Medical Service has voted its approval. The Blue Cross national insurance company is well on its way to completion. Sufficient capital funds have been raised and assurance of favorable action by the Illinois Commissioner of Insurance has been received.

The recent expansion (September 1, 1949) of the Blue Shield program to include nongroup enrollment was a significant step in the right direction. A previous effort in this regard, undertaken in June, 1947, was nullified by concurrent difficulties in which Blue Cross found itself.

Revision of the Blue Shield subscriber certificate (effective September 1, 1949) should go a long way toward clarifying administrative details. The provision that a member who uses private accommodations when such accommodations are not medically necessary is automatically classed as over-income will require judicious application by the medical profession.

Much dissatisfaction is reported by physicians with the restrictions and limitations on "existing" and congenital conditions in the Blue Cross subscriber contract. It also appears that patients are being forced to accept ward service because they are unable to pay the difference between the board and room rate at the hospital and the \$7.00 credit allowed by Blue Cross. This is also true of the differential between the \$70.00 provided by Blue Cross for maternity care and the hospitals' charges for this service. It is anticipated that the Society representatives on the Blue Cross Board of Directors will give these matters their serious attention.

Many requests that they be permitted to enroll themselves and their families in Blue Shield are being received from physicians. *It is recommended that this matter again be referred to the appropriate committee for consideration.*

PAUL M. BUTTERFIELD, M.D.
JOHN FALLON, M.D.
HARVEY A. KELLY, M.D.
JOSEPH C. MERRIAM, M.D.
CHARLES J. E. KICKHAM, M.D.

APPENDIX NO. 22

REPORT OF THE ADVISORY COMMITTEE TO THE WOMAN'S AUXILIARY

The Committee is happy to report that 12 of the 18 district auxiliaries are now organized and that over 1000 ladies are now active members.

The Auxiliary has already more than fulfilled the high hopes that were held for it. The ladies have shown excellent

interest and have participated capably and enthusiastically in furthering the efforts of the Society.

Much has been accomplished on the suggested sixteen point program for the Auxiliary outlined by the Committee in October, 1948, and presented to the Council at its February meeting.

Additional fields of activity have been reviewed and are offered to the Auxiliary for consideration and such action as may be indicated.

Continued efforts toward maximum enrollment in numbers of district auxiliaries and in individual memberships.

Co-operation with the phase of the National Education Campaign of the American Medical Association that pertains to the Auxiliary. Such activities may well include the training of speakers and arranging for their appearance before various women's groups, passage of appropriate resolutions by each of the district auxiliaries opposing the Administration's compulsory national tax sickness program, arranging for framing of colored reproduction of Sir Luke Fildes' picture "The Doctor" for display in physicians' offices, and distribution of national education campaign literature.

Sponsorship of "Career Days" in high schools throughout the state. Contact with school committees and school superintendents and principals should urge the value of presentation of the background of various trades and professions to high-school students about to seek employment or who intend to continue their education. Such programs indirectly aid the medical, nursing and other health professions by attracting the most competent and suitable candidates.

Co-operation with Medical and Surgical Relief Committee, Incorporated, in the collection of medical and surgical supplies for overseas hospitals and institutions that give free medical aid to the needy.

The Committee wishes to congratulate the officers and members of the Auxiliary for the excellent results they have accomplished. Under the presidency of Mrs. Leighton F. Johnson of Norfolk much progress was made in the first year. The annual meeting of the Auxiliary in Worcester in May was a distinct success.

To Mrs. Charles E. Ayers, of Worcester, and to her fellow officers for 1949-50 we wish every success in the continued growth and development of this valuable adjunct to the Society. The continued enthusiasm and active co-operation of the Auxiliary members are urgently needed.

DAVID L. BELDING, M.D.
MILTON J. QUINN, M.D.
JOHN F. CONLIN, M.D., Chairman

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D. *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35491

PRESENTATION OF CASE

A fifty-nine-year-old retired insurance salesman was brought to the hospital in a state of confusion and disorientation.

He had always been well until five months before admission, when on waking one morning, he was found to be confused and unable to recognize his wife. He had a thick, slurred speech and shortly afterward, during examination by a physician, he suddenly had a convulsive seizure. This began with a turning of the eyes upward and, it was thought, to the left and a drawing up of the left corner of the mouth, followed by clonic movements of both arms and legs, lasting two or three minutes. Three similar convulsions occurred in rapid succession. There was no incontinence and no biting of the tongue. After fourteen hours of unconsciousness the patient improved and was left with some thickening of speech and weakness of the extremities. He recalled a "snapping" feeling in the left frontal region the night before the onset of symptoms. There had been no headache. A month later he seemed to be in "perfect health." One month before admission he was again confused for a few minutes. During the next week he became "weaker" and complained of a sharp constant pain across the low lumbar region, which increased on coughing or sitting down but felt better on walking or lying. Ten days before admission, there was progressive weakness of the legs and eventually inability to walk. No numbness or paresthesia had been observed. He developed increasing constipation and a feeling of urgency and difficulty in voiding. Six days before admission his speech again became thick, and at times he was irrational. He developed a "rapid clonic tremor" of both hands and twisted and pulled at the bedclothes. He occasionally complained of diplopia, of pains and headache in the

right frontal region and "tingling" in the nose. Two days before admission he changed markedly for the worse, becoming excitable, voluble and completely confused. He had lost 15 pounds in the previous four months.

The past history was irrelevant except for occasional frontal headaches and a morning cough for the past five or six years. Recently he had taken one "phenobarb" and one or two "bromides" a day. Previous to his illness, nothing abnormal had been found at bi-annual insurance examinations.

Physical examination revealed a confused, disoriented, slightly euphoric man in no acute discomfort. There was incontinence of urine. A scaling erythematous eruption was seen over the face, chest and arms. There was a purulent nasal discharge, and the tongue was red and smooth. The heart sounds were slapping and of poor quality. The lungs and abdomen were normal. The neck and spine were rigid. There was well localized tenderness and bilaterally radiating pain on pressure over about the seventh thoracic vertebra. Midthoracic pain was also brought on by coughing. The cranial nerves were normal. Speech was slurred, rapid and indistinct, with some groping for words. There was slight weakness in the arms and scarcely any strength in the legs. The weakness was more marked on the right side. Pain sensibility was diminished over the legs and lower abdomen, but a definite level could not be made out. Vibration was felt over the malleoli. The tendon reflexes were difficult to obtain or were absent, and the findings of the different examiners did not agree in all respects. There was no agreement about the comparative activity of the arm jerks. Knee jerks were thought to be more active on the left. The ankle jerks, the abdominal reflexes and the plantar reflexes were absent, and on one occasion there was an equivocal extension reflex on the left. The pupils were equal and reacted normally on admission, but later the left was somewhat larger than the right. There was slight blurring of the nasal margins of the optic disks, thought to be not definitely abnormal. Confrontation fields were normal.

The temperature was 99.6°F, the pulse 85, and the respirations 84. The blood pressure was 140 systolic, 90 diastolic.

The red-cell count was 4,300,000, and the white-cell count 1500, with 78 per cent neutrophils. The bromide was 6.6 milliequiv, and the chloride 103.0 milliequiv per liter. The acid phosphatase was 1.9 units. A blood Hinton test was negative. The urine was normal. An electroencephalogram was diffusely abnormal. The initial spinal-fluid pressure was equivalent to 98 mm of water, with normal dynamics. The fluid was xanthochromic, clotted rapidly and contained 2 lymphocytes and 140 red cells per cubic millimeter. The total protein was 282 mg, the sugar 61 mg, and the chloride 641 mg.

per 100 cc The gold-sol curve was 0145555555 The Wassermann reaction was negative

X-ray films of the skull showed slight displacement of the pineal shadow toward the right A chest film was normal, except for minor degenerative changes in the spine

Six days after the lumbar puncture, combined cistern and lumbar punctures gave the following results cistern, initial pressure 210, jugular compression 350, release 250, xanthochromia +, lymphocytes 1, and protein 192 mg, lumbar, initial pressure 210, jugular compression 350, release 250, xanthochromia ++, lymphocytes 5, and protein 402 mg

The patient's course in the hospital was steadily downhill Four days after admission the temperature rose to 101.5°F, and rales appeared in the right axilla Penicillin and sulfadiazine were of no avail Voiding became progressively more difficult, and a Foley catheter was inserted On the eighth hospital day a skull trephination was performed Three days later another chest x-ray film showed patchy areas of increased density over both lower-lung fields The patient became flushed, dyspneic and lapsed into deep coma He died on the fourteenth hospital day

DIFFERENTIAL DIAGNOSIS

DR ROBERT SCHWAB* The left-sided seizure began with twitching on the left side of the face, which was said to have been observed by a local physician It might have been an error in observation It is difficult in a case of early seizure to be sure whether it involved the left or right side The left-sided seizure does not fit in with the neurologic findings It would seem from the original examination that this convulsion would if anything be a right-sided affair with aphasia Dr Cole assures me that I have a four-to-one chance that this patient was right-handed and therefore that the lesion was in the left frontal area That is where he had the snapping sensation, and the right side was weak It is much more reasonable to suppose that the original seizure began on the right side of the face and became generalized

The spinal-fluid findings and the laboratory findings are worth consideration at this point I should like to ask Dr Kubik about this because it is an important point in the differential diagnosis Is this a red herring or a misprint that there was a white-cell count of 1500?

DR CHARLES S KUBIK The white-cell count was 15,000

DR SCHWAB We have a striking abnormality in the spinal fluid in that the protein was increased to 282 mg per 100 cc On the first examination the pressure was said to be normal, and the fluid clotted rapidly, with normal sugar and no increase in cells, except a few red cells, which may have been the re-

sult of trauma The chlorides were down slightly, and I believe that could be explained by the increase in protein The normal sugar is evidence against infection in the meninges The gold-sol curve is a meningitic one, which is found in marked increase in albumin content as opposed to globulin The blood Hinton and spinal-fluid Wassermann reactions were negative

The second factor we will discuss along with the first one is the combined puncture in the lumbar and cisternal regions The marked increase in protein in the lumbar space over the cistern indicates a slight chemical block, but there was no evidence of dynamic block Again, no evidence of infection was noted, as indicated by the absence of white cells in the fluid The neurologic findings were absent knee jerks, slight weakness of the right side and slight papilledema, which is a further check of the protein of 282 mg per 100 cc During the second puncture, he complained of diplopia, and the x-ray films showed the pineal body shifted to the right

DR REGINALD LINGLEY As far as I can see, the films show only a displacement of the pineal body toward the right side There is no evidence of chronic pressure, and the sella turcica is normal

DR SCHWAB This is a very important sign, particularly with a good anteroposterior film such as this, and it indicates a space-occupying lesion in the left side of the cranium that would be consistent with right-sided weakness, the onset of convulsions on the right side, and the complaint of headache in the left frontal region We must not forget that this patient complained for some time (five months or so) of loss of weight, increasing constipation and pain in the back Also, at entry he had tenderness in the back in the same area That is impossible to correlate with a single lesion in the left frontal region So it seems to me that we have to start out by supposing we have two lesions a lesion in the spinal canal of some sort and a lesion in the left frontal area, perhaps of the same nature The most obvious etiology of the two lesions or multiple lesions is neoplasm I was seriously led by what I thought was a leukopenia to the consideration of a blood-cell tumor such as leukemia Hodgkin's disease sometimes invades the nervous system, causing lesions, so that the patient complains of central-nervous-system symptoms rather than generalized ones, and at autopsy one may find evidence of leukemia or Hodgkin's disease infiltrating the meninges But with the leukopenia removed, I am not so certain that that consideration is tenable A white-cell count of 15,000 would be reasonable for anyone admitted with chronic cough and some loss of weight One would suppose that there was involvement of the meninges around the spinal cord, giving a loss of ankle jerks, weakness of the legs and tenderness in the spine The other lesion in the frontal area, causing the original epileptic seizure

*Associate neurologist, Massachusetts General Hospital

and the stupor, could possibly produce intracranial pressure

Again coming to the consideration of the most plausible causes for lesions in two places, the commonest are tumors of the brain that are metastatic. Lung tumors have a high incidence of brain and spinal-cord involvement. This man had both loss of weight and chronic cough preceding entry. The presence of a smooth, red tongue and chronic infection might go with any debilitating illness and fit in with a carcinomatous condition if that were causing the two lesions of the central nervous system. I do not believe it likely at his age that he had multiple hemangiomas, they could cause a high spinal-fluid protein and could occur in more than one place. My first bet would be that it was a metastatic tumor, and my second one, a primary intracranial neoplasm that had spread directly down the spinal cord, down the meninges or with its own metastases. The third possibility is a blood-forming tumor such as leukemia or Hodgkin's disease, but we have no evidence for such a lesion. The condition was rapidly growing, in a man who was in reasonably good health three months before he came to the hospital. Before death he failed to respond to trephination and other exploratory measures in the hospital. My impression is that he had metastatic cancer in the brain and spinal cord.

DR AUGUSTUS S. ROSE: What is the explanation for the stiff neck?

DR SCHWAB: Involvement of the meninges in the spinal canal with neoplasm.

DR JAMES C. WHITE: One type of tumor in a man of this age that would give these symptoms is medulloblastoma.

CLINICAL DIAGNOSIS

Encephalitis?

Bronchopneumonia

DR SCHWAB'S DIAGNOSIS

Metastatic tumor in brain, left frontal region, and in spinal cord

ANATOMICAL DIAGNOSES

Glioblastoma multiforme of left temporal lobe, with metastases to spinal cord and spinal nerves

Bronchopneumonia

PATHOLOGICAL DISCUSSION

DR KUBIK: I believe that Dr Schwab's diagnosis is by far the most logical one. Multiple tumors of the central nervous system usually mean metastases, symptoms of which not infrequently appear before any prominent symptoms of a primary tumor have been noted. That is particularly true of bronchiogenic carcinoma.

This, however, was not carcinoma but another condition, which Dr Schwab also mentioned as a possibility — that is, a glioma with "metastases"

or implantations, which were disseminated through the subarachnoid space. Although this is not too uncommon in cerebellar medulloblastoma, it occurs quite infrequently with glioma of the cerebral hemispheres and is almost never diagnosed except when it is discovered at post-mortem examination.

The primary tumor, measuring approximately 6 cm in diameter, was situated in the left temporal lobe (Fig 1) below the Sylvian fissure, which was displaced upward. It invaded the inferior part of the lenticular nucleus, and, in the region of the hippocampus, it extended to the medial surface of the temporal lobe, where it broke through the pia and

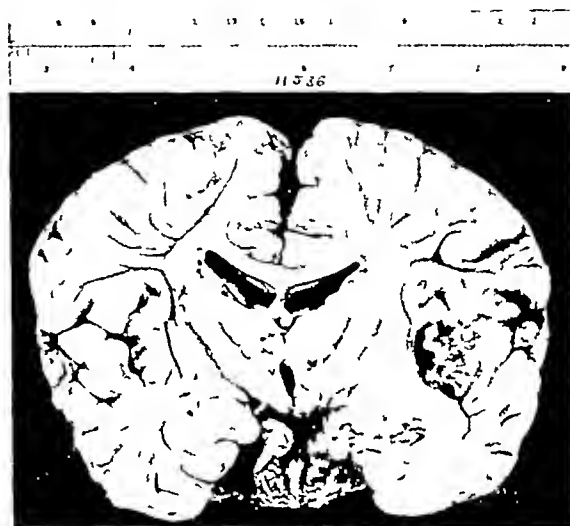


FIGURE 1 *Glioblastoma Multiforme, Left Temporal Lobe*

invaded the subarachnoid space. It was from here, presumably, that tumor cells floated through the spinal fluid to seed themselves in distant parts of the subarachnoid space.

There was one, measuring approximately 1 cm in diameter, on the dorsal surface of the spinal cord in the midthoracic region, and another, 1.3 by 0.8 by 0.2 cm, on the ventral surface in the upper lumbar region (Fig 2). These were the largest nodules; there were a number of smaller ones, including several on the roots of the cauda equina (Fig 2).

The tumor invaded the left third cranial nerve, thus explaining the enlargement of the left pupil.

There were two nodules, the larger one measuring 0.8 cm in diameter, on the surface of the right cerebellar hemisphere, and several on the spinal cord and spinal nerves.

There were no metastases to any other organs.

The primary tumor and implanted nodules were indistinguishable from each other in histologic appearance. Both were composed largely of slender

and plump fusiform cells with slender, elongated and broader, oval nuclei, which varied considerably in size. There were many multinucleated forms, a fair number of mitoses and numerous foci of necrosis. Connective-tissue and reticular stains revealed no stroma outside the blood vessels. The nodules

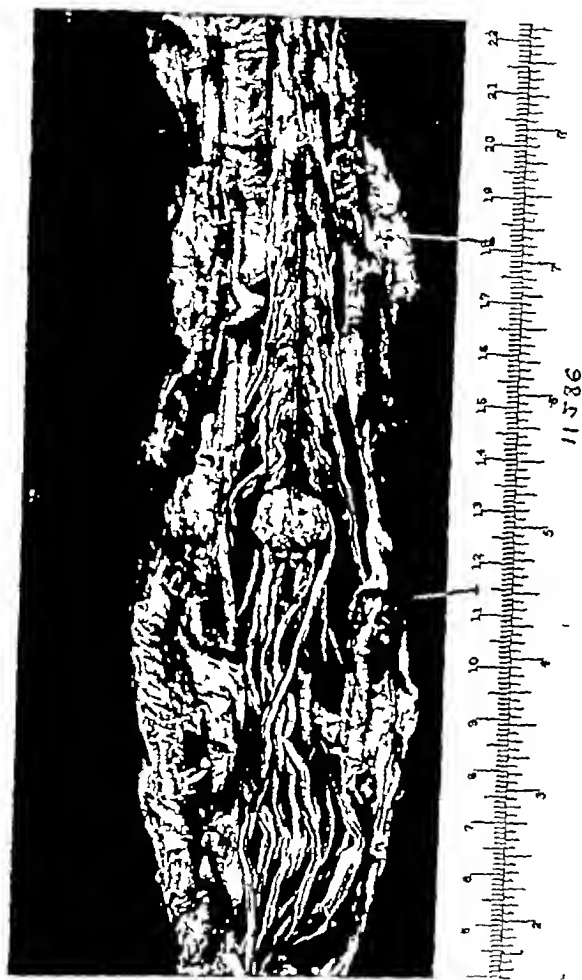


FIGURE 2 Metastatic Nodules on the Spinal Cord and Spinal Nerves

invaded the underlying spinal cord and adjacent spinal nerves and arachnoid membrane. In some places there was diffuse infiltration of the subarachnoid space by tumor cells without nodule formation.

The tumor was clearly a glioma, which I should classify as glioblastoma multiforme.

CASE 35492

PRESENTATION OF CASE

A fifty-nine-year-old man was admitted to the hospital complaining of repeated hematemesis during the preceding twenty-four hours.

About five years before admission the patient began to have two-day to three-day periods of "indigestion" characterized by sharp epigastric pain, bloating and sour eructations coming on two or three hours after a meal, relieved by soda but not by food. The day before admission he noted the sudden onset of warmth, sweating and weakness, and he vomited about a liter of dark blood and clots without any pain or nausea. He was given a hypodermic injection by a physician and remained in bed for the rest of the day without any further symptoms. On the day of admission at about 4:45 a.m., he was awakened with a second hematemesis and shortly afterward passed a large, tarry stool. At 6:00 a.m. and again at 9:00 a.m. he also vomited blood, and arrived at the hospital in moderate shock.

The past and family histories were noncontributory.

Physical examination showed a well developed, moderately well nourished man. The skin was pale, cold and clammy. The abdomen was soft, with an ill defined, nontender mass, 6 by 8 cm., in the right upper quadrant.

The temperature was 100.6°F, the pulse 94, and the respirations 22. The blood pressure was 88 systolic, 68 diastolic.

The urine was normal. The hemoglobin was 8.5 gm per 100 cc. The prothrombin time was 57 per cent of normal. The nonprotein nitrogen was 78 mg., and the total protein 5.2 gm per 100 cc. A limited gastrointestinal series on the third hospital day showed no evidence of esophageal varices or tumor, but revealed widened gastric folds, an inconstant duodenal deformity and a questionable crater.

The patient received 2500 cc of blood on the first hospital day, with a rise in hemoglobin to 11.5 gm. Transfusions of 500 cc per day were continued, but he remained weak and hypotensive. Therefore, on the sixth hospital day, after preparation with Hykinone and further transfusion, a subtotal gastrectomy was performed. Pathological examination of the specimen showed only mild chronic gastritis. The patient did well until the second postoperative day, when he began to vomit small amounts of blood, and blood was noted in the gastric drainage tube. This persisted until the sixth postoperative day, when there was massive hematemesis of 2400 cc with resultant hypotension and incipient shock. Following this he was re-explored.

DIFFERENTIAL DIAGNOSIS

DR. PERRY CULVER* We are presented here with the problem of the differential diagnosis of upper-gastrointestinal-tract hemorrhage that was sufficient to put a man into shock. The age is that of a person who could have cancer, ulcer, gastritis,

*Assistant in medicine, Massachusetts General Hospital

varices or anything else, so I do not think the age is going to help to any extent.

The five-year story of indigestion is a vague one. This symptom could have been due to ulcer, and the epigastric pain would also be in keeping with such a diagnosis. Ulcer would also explain the bleeding and sour eructations. It is unusual for food not to relieve ulcer pain but it does not always do so in every case. I think that fact is of importance in this case, however. The nebulous diagnosis of gastritis is one that continually pops up in a situation like this. There is a great deal of argument about whether gastritis may cause symptoms. Enthusiasm for this diagnosis waxes and wanes. At times people have had the impression that symptoms of gastritis were not due to gastritis but to some underlying condition. On the other hand, we have seen cases of gastritis sufficiently severe to cause profuse bleeding without any symptoms whatsoever. The textbooks will tell one that the symptoms of gastritis are those of peptic ulcer except that food does not relieve gastritis. If one wishes to accept textbook experience, gastritis fits this case perfectly — ulcer pain not relieved by food. That is a rather weak nail to hang one's hat on, but I mention it in passing.

It is of interest to speculate upon what part of the symptoms may be attributed to a nervous stomach, but it is unusual for nervous-stomach symptoms, whatever they are to appear at this age. They occur usually in much younger persons. I think this patient had an organic disease. A nervous stomach does not cause hemorrhage. It is a little unusual for cancer of the stomach to bleed so massively, and the history of a five-year period of indigestion would make me less likely to favor cancer.

These are the main diseases that I can think of that might cause both symptoms of this nature and hemorrhage. I will take up other causes of hemorrhage when we come to the x-ray studies.

The history, subsequently, was that of massive hemorrhage with shock. No further comment is needed on that. I would like to know one thing about the past history — that is whether there was any history of alcohol intake.

DR TRACY B. MALLORY: I remember seeing a statement that the patient was a moderate drinker.

DR CULVER: That can mean anything.

The physical examination as we might expect in most of these conditions, with the exception of cancer, is of little help. Certainly, ulcer and gastritis cannot be diagnosed on the basis of physical examination. I am very much puzzled about the mass described here. It was 6 by 8 cm. in the right upper quadrant. Does it have anything to do with the diagnosis? Is it a clue, or is it a bit of information that has nothing to do with the case and is a red herring. For the time being, I am going to disregard that mass.

DR MALLORY: Perhaps Dr. Donaldson would be able to give some information about that.

DR GORDON A. DONALDSON: The finding is more prominent in the history than it actually was.

DR CULVER: I was going to ask whether the X-ray Department could see it.

DR DONALDSON: I never felt it. It was a rather vague, indefinite mass.

DR CULVER: I will dismiss it as of no consequence. The laboratory tests were those of marked blood loss, as one would expect. The prothrombin time of 57 per cent was not in the range that is usually considered low enough for bleeding, a prothrombin time of about 20 per cent is the critical level. A prothrombin time below this level is often a factor in prolonged bleeding. We do not have information suggestive of other blood dyscrasias or of disturbances in the clotting or bleeding mechanism. I am inclined to think that such conditions are not involved in this case. A prothrombin level of 57 per cent may indicate that the diet is not quite adequate in vitamin K or that the liver lacks the power to manufacture prothrombin. Have we anything to indicate what the prothrombin time was after Hylanone administration? Is there more information about studies of liver function? They are more of academic interest and do not contribute to the differential diagnosis. The nonprotein nitrogen of 78 mg. per 100 cc. with an apparently normal kidney function leads me to believe that this azotemia was not due to renal failure, and that uremia was not playing a role in the cause of bleeding. The elevated nonprotein nitrogen was due probably to dehydration plus blood in the bowel. In this case, we have to depend upon the x-ray films, possibly gastroscopy, and, finally, an exploratory laparotomy. Review of the x-ray films is the next obvious move.

DR STANLEY M. WYMAN: All the films we have were taken on the original examination. They are spot films. The patient was very sick, and we were not able to keep him in the department long enough to take conventional large films. The esophagus, however, is well seen and appears normal. There is a definite suggestion of a hiatus hernia on at least one spot film. The stomach itself is not entirely visualized, but on these two films the gastric folds are seen to be more prominent than usual in a diffuse manner.

DR CULVER: Would you want to say that widening of gastric folds is consistent with the diagnosis of chronic hypertrophic gastritis? Is the widening marked enough for that?

DR WYMAN: I do not believe we can make that diagnosis with any degree of certainty. We have seen the same picture in a patient with atrophic gastritis proved by gastroscopy. The mucosa was parchment thin, and yet the picture was identical with this. This is what one sees with hypertrophic gastritis, but I do not believe such a diagnosis

can be made with certainty. The duodenal cap is only partially visualized, and I can make no definite statement about it. I do not see a crater. All in all, the examination is very incomplete of necessity. I think it leaves many questions completely unanswered.

DR CULVER: I think it helps in ruling out esophageal varices. It helps us to eliminate cancer of the stomach and gastric ulcer. Would you agree to that?

DR WYMAN: And it reveals the hiatus hernia.

DR CULVER: Yes, that is an important bit of information and one that I should have considered in the differential diagnosis of things that might cause symptoms in the epigastrium. There is no mention that lying down made the symptoms of indigestion worse than sitting up.

From the x-ray films I think we are still in the dark about the cause. We obviously could not rule out ulcer completely by gastroscopy because the patient was too ill for such a procedure.

I take it that the third form of further diagnostic measure was necessitated as an emergency procedure. At exploration, if I may project myself into the mind of the surgeon, he may or may not have found a scarred duodenal cap. I suspect that he did not, and considered that there was hemorrhage from the stomach. I do not know what he saw when he opened the stomach, but perhaps he found a diffusely inflamed stomach with no definite bleeding point but with a generalized ooze consistent with the type of bleeding seen in gastritis. The usual treatment for gastritis that causes massive bleeding, and these patients can bleed massively, is a subtotal gastrectomy.

The possibility of some obscure cause of bleeding has to be considered here. One thing may be gastric varices. There is nothing to help make that diagnosis. Gastric varices can occasionally occur without esophageal varices. Another rarity is telangiectasia involving the stomach, with bleeding from a telangiectasis. This man was too old. There was no history and no suggestion of telangiectasis on physical examination. We can forget that.

We can come back again to gastritis or ulcer. There is the possibility of bleeding gastritis in the hiatus hernia, and sometimes hiatus hernia can become strangulated. The resulting congestion causes it to bleed. The patient had an operation, and then he started to ooze on the second postoperative day and continued to ooze. That makes me think, more and more, that the lesion was probably in the remaining portion of the stomach as well as in that portion of the stomach resected. Was this continued bleeding arterial in type? Arterial bleeding, such as that from a bleeding ulcer, should be massive, and it ceases as the artery contracts. In this case the continuous bleeding makes me suspect the capillary type, which would be consistent with gastritis in the remnant of stomach,

possibly in a portion of stomach caught in the hiatus hernia.

There is one other possibility, and I am sure it entered the surgeon's mind on the sixth postoperative day when the patient had a massive hematemesis. It is the possibility of a suture sloughing off an artery with a hemorrhage from that source. It is something to be considered, and I suppose the surgeon might want to look for that.

Finally, if there were an ulcer and a subtotal gastrectomy did not include the ulcer, I suppose there could be further oozing and massive hemorrhage from that source. Such a possibility seems unlikely, or the surgeon would have done something other than a subtotal gastrectomy for this ulcer when the patient was bleeding.

The most likely diagnosis is hemorrhage from gastritis in the gastric remnant. I doubt if the mass described in the protocol was ever found.

DR DANIEL S. ELLIS: Do we know what was found at the time of the first operation?

DR DONALDSON: This patient was on the wards for about ten days and called forth a tremendous amount of effort on the part of the House Staff. He was given twenty-five or thirty transfusions. The excuse for not having more adequate laboratory studies was that at each turn our hand was forced because of the bleeding. The first gastrointestinal series was done on a Sunday morning in an attempt to find a bleeding point. Our diagnosis before the first operation was gastritis. Gastritis causes about 5 per cent of massive hemorrhage in this hospital. We were also worried about the definite hiatus hernia and the questionable duodenal defect as shown in the x-ray picture.

At the time of operation there was a great deal of old blood in the small bowel. The duodenum did have a scar on the anterior wall just beyond the pylorus. The stomach, itself, was somewhat thickened. There was a definite hiatus hernia. With these findings we thought that our preoperative diagnosis was probably still right. We went ahead and did a subtotal gastrectomy. At the time the upper segment of stomach was explored, the clamp was removed, and with retractors in place we were able to look and feel around inside. The mucosa was thickened, and the rugae were coarse. We could find no bleeding point. No blood was found in the segment at that time, and we still thought that we were dealing with gastritis — and so completed the operation.

One unusual fact that was noted by the men at the table was that the arteries were unusually arteriosclerotic — the gastroduodenal particularly. The second operation was forced on us by the subsequent massive hemorrhage.

DR ELLIS: Did you resect the scar?

DR DONALDSON: Yes, it was just beyond the pylorus on the anterior wall and was resected. When the subsequent massive hemorrhage occurred,

the patient was in such straits from blood loss that we attempted to control the bleeding by placing a balloon in the stomach segment and by applying traction on the end of the tube as it escaped from his nose. We thought we had stopped the hemorrhage long enough to allow us to operate on him. This led us to believe that the bleeding came from the hiatus hernia or nearby, certainly. He was taken to the operating room in this condition, and exploration was carried out through the chest. There were no varices on the gastric wall, and again the arteries were noted to be unusually sclerotic — the left gastroepiploic and the left gastric itself. We did not open the stomach, but went ahead and took out the remnant and anastomosed the esophagus to the jejunum, taking down our previous resection.

DR MALLORY Have you any further opinion Dr Culver?

DR CULVER I think it still has to be gastritis but I am probably wrong.

DR ELLIS Would you consider the possibility of stomal ulcer in six days?

DR CULVER It was too soon for a stomal ulcer, which usually develops in four or five weeks. With the history of arteriosclerosis as striking as Dr Donaldson suggests, I am more inclined to think of the possibility of a ligature eroding through a blood vessel and causing bleeding.

DR DONALDSON That is a good possibility and we considered it. The fact that the balloon stopped the bleeding made us feel better about it.

DR CULVER I still think it was gastritis.

CLINICAL DIAGNOSES

Gastric hemorrhage from arteriosclerotic vessel
Subtotal gastrectomy
Resection of gastric remnant

DR CULVER'S DIAGNOSES

Gastritis
Gastric artery eroded by ligature

ANATOMICAL DIAGNOSIS

Cirroid aneurysm of branch of left gastroepiploic artery, with rupture and massive hemorrhage

PATHOLOGICAL DISCUSSION

DR MALLORY In the second resected specimen we found a very definite bleeding point (Fig 1)

The first specimen showed only mild gastritis. This is the second, showing that the mucous membrane is shallowly eroded, but the erosion extends into the wall of a large sclerotic artery. There is a fresh thrombus at the point of erosion. Even in this very small section, not much more than a cm in length, the artery has been cut across four different times, indicating that it was very tortuous and must be classified as an arteriosclerotic cirroid aneurysm. This is not an extremely rare source of massive gastric hemorrhage. This is, I believe, the



FIGURE 1

third case that we have had with essentially the same picture.

A PHYSICIAN Where in the stomach was it located?

DR MALLORY Close to the lesser curvature.

DR DONALDSON In retrospect, I would like to ask if gastritis would cause hemorrhage without any previous bleeding of a mild nature. We thought afterward that it might have helped.

DR CULVER Four cases were reviewed by Dr Fairlie last spring. All 4 patients bled massively, and no explanation other than gastritis was found. Some bled fairly acutely. In each of these, some other cause may have been missed. I think the whole problem of diagnosis of gastritis and the significance of gastritis is still open to question. But on the basis of experience, I would say that perhaps it could cause hemorrhage, as in this case.

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MAN VERSUS THE GOOD EARTH

THE REVEREND THOMAS MALTHUS died suddenly of heart disease at sixty-eight a little over a hundred years ago. He was much abused, though a gentle character personally, because of his ominous warning that "population has a tendency to increase faster than food." The fear of world-wide hunger, however remote, has been present ever since. Neo-Malthusians can point to the threefold increase in world population in the past hundred years (at the moment, possibly at the rate of 20,000,000 a year), and to the 1,000,000,000 underfed of the earth's 2,250,000,000 people. Here in the United States although the divorce rate and the fertility per family are viewed with alarm and worry about letting in or keeping out displaced persons and disagreement about birth control are

widespread, the Government has been aggressively wooing the friendship and seeking to influence a man and a nation with a real population problem. If Nehru's India continues to increase its present 355,000,000 at a rate of several million a year, its problem will be that of the United States as well, to say nothing of a 12,000,000 increase in the European population despite an estimated total war loss of 30,000,000. Furthermore world-wide sanitation, production of new and better antibiotics and new antimalarial drugs are eliminating "nature's pruning hooks."

Some astonishing and somewhat unpleasant facts are submitted by Calder* in a British country newspaper. The British are strictly dependent upon food from overseas and are therefore properly concerned about wastage anywhere, whether in Africa or Australia or the United States. The famous methods of production of this country are, in some agricultural cases, infamous methods of waste "soil unbroken for a thousand years in Oklahoma was lost in a single generation."

Americans are chagrined to be reminded of their erosion problem and its absence in countries intensively cultivated for generations. It is chastening to learn, moreover, that a British farmer can get twice as much wheat from an acre as an American farmer and four times as much as an Australian. For the American and for the Australian the problem is too few persons on the land. Erosion is not "due to overworking but to undernursing." In India, where the problem is too many on the land, the anticipated industrialization will draw people from the land and not only offer but also demand modern methods of intensive cultivation and conservation since modern medicine and sanitation are committed to increase the life expectancy at birth in Eastern countries, which is now only half that in the United States.

Medical scientists need to familiarize themselves with some new terms, such as "biotic potential" (soil yield in terms of living growth for the use or comfort of man) and "environmental resistance" (unfavorable climate or man's abuses, or both). As world citizens, Americans applaud the Nobel committee for its award of the peace prize to John

*Calder, R. World food resources. *The Field* London, August 27 1949

Boyd Orr, the distinguished Scottish agricultural economist. He is reported as one of those "who say that with science and common sense the world could feed twice and twice again, its present population." Perhaps, as Calder hopefully adds, if biotic potential can be made to match environmental resistance, "the world can nourish, clothe, and house as many people as the human race can produce." Should this end be achieved, men of Lord Orr's stamp will be needed since, aside from guiding the United Nations Food and Agricultural Organization, he is head of the World Federalists.

PILOT CLINIC

SEVEN months ago, when the principle of the health-protection clinic was first discussed in these pages, the proposition was looked upon in various quarters with considerable doubt and some disfavor. Even such specific and circumscribed propositions as cancer-detection clinics were encountering heavy weather in their efforts toward general acceptance, and the combining of isolated screening procedures so that they could be done on the same patient in one place and at the same time seemed altogether too radical.

The acceptance of pilot studies that might at least explore the debated area seemed not too wide an entering wedge, however, and so it was voted by the Council of the Society at its annual meeting on May 23. The progress that has been made in the short time elapsed since then speaks for the alacrity with which the able subcommittee on pilot clinics has acted, and the interest shown in the proposal by other agencies.

A preliminary report of the subcommittee appears in the Massachusetts Medical Society column in this issue of the *Journal*. A first "multiphasic screening clinic," to employ the somewhat redundant terminology offered by science, has already been established at the New England Center Hospital, and a trial run to break in the machinery has just been completed. As New Year, 1950, fades into history, the bona fide test of the clinic will begin.

SCHOOL PHYSICIANS MOBILIZE

ACTING on the time-tested principle that "united we stand," and having read the writing on the blackboard, the school physicians of Massachusetts have banded themselves together into their own organization. Such a union is long overdue and in the very nature of its purposes is a praiseworthy undertaking.

Formed in order "to work for the betterment of school health services, to encourage the meeting together of school physicians in Massachusetts, to exchange experiences and to discuss problems pertaining to any phase of school health service, and to promote a better understanding between the school physicians and the community," the Association cannot but add dignity and prestige to a very vital medical responsibility.

Obviously only a small percentage of school physicians are employed on a full-time basis, in most communities part-time service is all that is required or needed. All the more necessary is it for the school physician, then, to look upon this segment of his activities not as a pot-boiling auxiliary appendix to his major income-producing labors, indifferently accepted and grudgingly discharged, but as a specialized and valuable department of practice.

It is understandably hard to eradicate from the medical mind, filled with the traditions of the physician as one devoting many and long hours to the care of the sick, the idea of bedside practice as his only really noble function. The austerity of medical science came early to share this admiration, but public-health practice in its various aspects, and administrative and industrial medicine have been more slowly accepted as suitable fields wherein the first-class doctor might deploy his talents.

The nation is undoubtedly interested in the improvement of school health services, and so long as the Association of School Physicians of Massachusetts (itself in its infancy) whole-heartedly follows this single aim, its members will find themselves engaged in a specialty that commands universal respect.

POLIOMYELITIS FUNDS DIMINISHED

A RECENT communication from The National Foundation for Infantile Paralysis, Inc., calls attention to the mounting costs of hospital care for the victims of this disease and the critical state that the financial burden to the Foundation has reached.

This situation has been brought to a head by the epidemic of 1949, as a result of which, for the first time in its eleven years of existence, the Foundation found it necessary to conduct a not altogether successful emergency drive for funds.

Despite the Foundation's continuing support of research and education, the payment for medical care to patients is its greatest expense, and this expense is particularly for hospitalization. Practicing physicians are consequently urged to care for patients with abortive, nonparalytic and mildly paralytic cases in the home, and to avoid prolonged hospitalization for the others. Funds for the "free" care of poliomyelitis patients are low, the dimes will not march again until February, and unnecessary expenses must be avoided.

Messrs Editors, — By the bearer we send you a specimen of diseased lung, which you may call encysted tubercle, osseous composition, or any other name your sense of propriety may dictate, after examining it

Boston M & S J, December 5, 1849

MASSACHUSETTS MEDICAL SOCIETY



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At the annual meeting of the Council of the Society held on May 23, 1949, a motion submitted by the Committee on Public Health approving the establishment in the Commonwealth of not more than five pilot health-protection clinics was adopted. It was further recommended that a subcommittee of the Committee on Public Health be appointed to develop and carry out such a program. This subcommittee was accordingly appointed, consisting of a representative from each of the 18 district medical societies under the chairmanship of Dr. John J. Poutas.

The subcommittee and its executive committee have subsequently held several meetings, with the following results:

The decision has been made to develop a single initial pilot health-protection or "multiphasic screening" clinic. This clinic has been set up at the New England Center and the Joseph H. Pratt Diagnostic Hospital. A local project committee has been established to determine local problems, and a central guiding committee has been set up to act in an advisory capacity.

Dr. Claire F. Ryder, of the Massachusetts Department of Public Health, has been appointed as administrator of the clinic.

It has been decided that, to perform its functions satisfactorily, the Clinic should run for approximately six months, operating four times a week. During this period it should be possible to examine 2000 to 3000 persons, a number that would constitute an impressive sample.

The proposed budget for such a clinic, including adequate pay for the participating personnel, will be \$31,000. The United States Public Health Service will consider this a co-operating clinic and will supply funds to be paid directly to the persons employed in the clinic up to an amount not exceeding \$15,000. Approximately \$12,000 is available through the services and funds of the Massachusetts Department of Public Health, and the remainder is to be raised from the voluntary agencies that have indicated their desire to participate.

Already, since the first of December, a trial run of approximately 100 personnel of the Department of Public Health has been made, extending through four clinic periods, without utilizing any of the funds earmarked for the actual clinic operation, which will begin after the New Year.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1949

DISEASES	RÉSUMÉ		
	OCTOBER 1949	OCTOBER 1948	SEVEN YEAR MEDIAN
Chancroid	0	2	2*
Chicken pox	307	622	370
Diphtheria	12	28	19
Dog bite	891	739	812
Dysentery bacillary	15	5	32
German measles	39	47	52
Gonorrhea	221	284	413
Granuloma inguinale	0	1	1*
Lymphogranuloma venereum	0	1	16
Malaria	1	660	508
Measles	107	6	11
Meningitis meningococcal	4	3	3
Meningitis Pfeiffer bacillus	0	2	2
Meningitis pneumococcal	0	0	0
Meningitis staphylococcal	0	0	0
Meningitis streptococcal	8	7	3
Meningitis undetermined	210	485	350
Mumps	244	31	65
Poliomyelitis	24	7	13
Salmonellosis	113	243	372
Scarlet fever	132	141	390
Syphilis	148	171	230
Tuberculosis pulmonary	7	11	16
Tuberculosis other forms	1	2	3
Typhoid fever	3	2	3
Undulant fever	314	180	460
Whooping cough			

*Five-year median

COMMENT

The only diseases above the seven-year median for October were poliomyelitis and salmonellosis.

Diseases below the seven-year median included chicken pox, diphtheria, bacillary dysentery, German measles, measles, mumps, scarlet fever and whooping cough.

Although the incidence of poliomyelitis dropped markedly from the high figures for August and September, cases were at the third highest ever reported in October.

Twenty-four cases of salmonellosis this month was the highest ever recorded in October, but in August this year there were 74 cases.

For the second consecutive month, measles was at the lowest level since 1957.

For the fourth consecutive month scarlet fever was at the lowest level ever recorded.

Although whooping cough was still below the seven-year median, this was the seventh successive month in which more cases were reported than in the corresponding month in 1948.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Boston 7 Burlington 1 Rockport, 1, Somerville, 2, Watertown 1 total, 12

Dysentery, bacillary, was reported from Boston, 7, Cambridge, 7, Wrentham, 1, total, 15

Encephalitis, infectious, was reported from Newburyport 1, Springfield, 1, total, 2

Infectious hepatitis was reported from Lawrence, 3 total 3

Malaria was reported from Gloucester, 1, total 1

Meningitis, meningococcal, was reported from Boston 1 Haverhill, 1, Maynard, 1, Peabody, 1, total, 4

Meningitis, Pfeiffer-bacillus, was reported from Attleboro, 1, total, 1

Meningitis, undetermined, was reported from Boston 2 Chelmsford, 1, Fall River, 4, Medford, 1, total, 8

Poliomyelitis was reported from Abington, 3 Adams, 2 Arlington, 3, Attleboro, 3, Auburn, 1, Barre, 2, Belmont, 1, Beverly, 1, Billerica, 2, Boston, 27, Braintree, 3 Bridge-

water, 1, Brockton, 1, Brookline, 3, Burlington 1, Cambridge, 3, Chelmsford 1, Chelsea, 3 Chicopee, 1, Dedham, 1, Deerfield, 2, Dennis, 1, Dover, 1, Dracut, 2, Duxbury, 1, East Bridgewater, 1, Fall River, 3, Falmouth, 1 Framing-

ham, 6, Franklin, 1, Gardner, 1, Great Barrington, 1, Hampden, 1, Hanover, 1 Haverhill, 2, Hingham, 1 Hinsdale, 1, Holbrook, 1, Holliston, 3, Hudson, 2, Lawrence, 1 Lee, 1, Leominster, 2, Longmeadow, 1, Lynn, 12, Lynnfield, 2, Malden, 3, Mansfield, 2, Marblehead, 1, Marshfield, 2, Mattapoisett, 2, Medford, 7, Melrose, 3 Middleboro, 1, Milford, 3, Millville, 1, Nantucket, 1, Natick, 1, Needham,

2, New Bedford, 6, Newburyport, 1, Newton, 8, North Adams, 1, North Attleboro, 1 Palmer 1 Pittsfield, 3 Plainville, 1, Quincy, 5, Reading, 4, Rehoboth 1 Revere, 3 Salem, 4, Salisbury, 1, Saugus, 1, Scituate, 1 Sharon, 1, Somerville, 5, Southboro, 2, Springfield, 3 Sterling, 3 Stoughton, 1, Swampscott, 1, Swansea, 1, Taunton, 2 Templeton, 1, Topsfield, 1, Walpole, 2, Waltham, 5, Water-

town, 3, Webster, 1, Wellesley, 6, Weymouth, 4, Whitman, 1 Williamstown, 2, Wilmington, 1, Winchendon, 5, Winchester, 1, Winthrop, 2, Worcester, 4, total, 244

Salmonellosis was reported from Amesbury, 2, Andover, 2 Boston, 8, Cambridge, 1, Everett, 1, Haverhill, 3, Lowell, 3, Malden, 2, Newton, 1, Salem, 1, total, 24

Septic sore throat was reported from Boston, 2, Lynn, 1, Medford, 1, Westford, 1, total, 5

Trichinosis was reported from Boston, 1, Cambridge, 3 Fitchburg, 1, Natick, 1, total, 6

Typhoid fever was reported from Chilmark, 1, total, 1

Typhoid fever was reported from Somerville, 1, total, 1

Undulant fever was reported from Agawam 1, Lincoln, 1, Pepperell, 1, total, 3

CORRESPONDENCE

MAINE MARITIME ACADEMY CRUISE

To the Editor Last year about this time I wrote to you for assistance in obtaining a medical officer for the annual cruise of the "American Sailor," training vessel for the Maine Maritime Academy. We are again making a cruise during the winter months to the Caribbean and Gulf of

Mexico and are in need of a doctor. Therefore, I am writing to request that you inform your readers of this opportunity for a cruise under very pleasant circumstances. For your ready information I will repeat the substance of my letter of last year which is also applicable now.

The training ship is provided by the United States Maritime Commission and is a very comfortable 400-foot steamer equipped as a training vessel with excellent medical equipment on board. Embarked will be the cadets, faculty and staff of the Academy, amounting to 220 persons. It has been the custom in the past to employ a doctor for this cruise which is tantamount to a vacation for him, owing to the fact that all persons on board are in excellent physical condition. However, we do desire a doctor on board in case of emergencies.

The pay is \$530 a month plus maintenance.

The cruise begins on January 12 and ends on March 26, 1950.

W W WARLICK
Rear Admiral USN (Ret.)
Superintendent

Maine Maritime Academy
Castine, Maine

BOOK REVIEW

The Basic Neurosis: Oral regression and psychic masochism
By Edmund Bergler, M.D. 8", cloth 353 pp. New York: Grune and Stratton, Incorporated, 1949. \$5.00.

Dr. Bergler, a Freudian psychoanalyst, and a prolific psychoanalytic writer, is well known among psychiatric circles by his papers and books dealing with common sexual problems and their influence on human behavior.

In his most recent work, Dr. Bergler has attempted to demonstrate why he believes that all neuroses if adequately examined and interpreted, will reveal the basic structure of oral regression and psychic masochism. Approximately the first half of the book is groundwork outlining concepts that are presented in the form of clinical pictures in the last half.

The author evidently assumes that the reader is familiar with basic psychoanalytic concepts and tenets because he immediately launches into his writing with terminology that is not necessarily basic. Also the use of the personal pronoun "I," especially in comparison with the name of Dr. Freud, appears to be a bit overdone to have the book in truly good taste.

In the chapter, "Orality and the Myth of the Superior Male," Dr. Bergler appears to have been provoked by editors, publishers and so forth, to whom he variously refers as neurotics of one form or another. This is evidently a contradiction and places him in the neurotic, easily provoked group as indicated from his title entitled "The Nine Point Basis of Every Neurosis" in the third chapter. To clarify this point further it is obvious that the author has used the fifth chapter as a direct retort to the people mentioned above, who obviously provoked aggression and disturbed his ego functioning. This chapter, in its present form, could have been, from the reader's standpoint, profitably omitted.

Aside from these criticisms the book is an excellent presentation of the mechanisms of orality and their influence on personality development.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Pain Syndromes: Treatment by paracervical nerve block
By Bernard Judovich, M.D., instructor in neurology, University of Pennsylvania School of Medicine, and physician-in-charge, Neuralgia Clinic, Graduate Hospital, Philadelphia, and William Bates, M.D., professor of surgery, University of Pennsylvania School of Medicine, consulting surgeon, Babies' Hospital and Philadelphia Home for Incurables, and

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At the annual meeting of the Council of the Society held on May 23, 1949, a motion submitted by the Committee on Public Health approving the establishment in the Commonwealth of not more than five pilot health-protection clinics was adopted. It was further recommended that a subcommittee of the Committee on Public Health be appointed to develop and carry out such a program. This subcommittee was accordingly appointed, consisting of a representative from each of the 18 district medical societies under the chairmanship of Dr John J Poutas

The subcommittee and its executive committee have subsequently held several meetings, with the following results

The decision has been made to develop a single initial pilot health-protection or "multiphasic screening" clinic. This clinic has been set up at the New England Center and the Joseph H Pratt Diagnostic Hospital. A local project committee has been established to determine local problems, and a central guiding committee has been set up to act in an advisory capacity

Dr Claire F Ryder, of the Massachusetts Department of Public Health, has been appointed as administrator of the clinic

It has been decided that, to perform its functions satisfactorily, the Clinic should run for approximately six months, operating four times a week. During this period it should be possible to examine 2000 to 3000 persons, a number that would constitute an impressive sample

The proposed budget for such a clinic, including adequate pay for the participating personnel, will be \$31,000. The United States Public Health Service will consider this a co-operating clinic and will supply funds to be paid directly to the persons employed in the clinic up to an amount not exceeding \$15,000. Approximately \$12,000 is available through the services and funds of the Massachusetts Department of Public Health, and the remainder is to be raised from the voluntary agencies that have indicated their desire to participate

Already, since the first of December, a trial run of approximately 100 personnel of the Department of Public Health has been made, extending through four clinic periods, without utilizing any of the funds earmarked for the actual clinic operation, which will begin after the New Year

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1949

DISEASES	Résumé		
	OCTOBER 1949	OCTOBER 1948	SEVEN YEAR MEDIAN
Chancroid	0	2	2*
Chicken pox	307	622	370
Diphtheria	12	28	19
Dog bite	891	739	812
Dysentery, bacillary	15	5	32
German measles	39	47	52
Gonorrhea	221	284	413
Granuloma inguinale	0	1	1*
Lymphogranuloma venereum	1	1	16
Malaria	107	660	508
Measles	4	6	11
Meningitis meningococcal	1	3	3
Meningitis Pfeiffer bacillus	0	2	2
Meningitis pneumococcal	0	0	0
Meningitis staphylococcal	0	0	0
Meningitis streptococcal	8	7	3
Meningitis undetermined	210	485	350
Mumps	244	31	65
Poliomyelitis	24	7	13
Salmonellosis	113	243	372
Scarlet fever	132	141	390
Syphilis	148	171	230
Tuberculosis pulmonary	7	11	16
Tuberculosis other forms	1	2	3
Typhoid fever	3	2	3
Undulant fever	314	180	460
Whooping cough			

*Five year median

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THE VALUE OF THE THORACOABDOMINAL INCISION IN THE REMOVAL OF KIDNEY TUMORS*

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BOSTON

ALTHOUGH the kidneys are situated below the diaphragm, they lie to a large extent within the thorax, sheltered by the lower ribs. Chiefly because the unyielding bony thoracic cage frequently bars the way to a free and satisfactory surgical exposure of the upper portion of the kidneys when they are enlarged, the lumbar extraperitoneal incision commonly used for renal surgery with or without removal of the twelfth rib, and also the transperitoneal approach often leave a great deal to be desired in the way of exposure when one is dealing with large tumors of the kidney. While searching for an incision that would give better access to and exposure of the kidney and retroperitoneal region, we contemplated using the thoracoabdominal incision. This type of incision in its present form is relatively new. One reason for this is that for its safe performance intratracheal anesthesia with the ability to exert positive pressure on the lung is essential, and this advance in anesthesia has come into use only during the past fifteen years. General knowledge concerning the handling of thoracoabdominal wounds and the use of thoracoabdominal incisions was given a great impetus by the surgical experiences of World War II. During the war one of us (L.S.) removed several traumatized kidneys by this route, which was also utilized by others.^{1,2} Although the thoracoabdominal incision has not come into general frequent use in the last few years it has been used for gastrectomy and esophagectomy, for carcinoma,³⁻⁵ for splenorenal anastomosis⁶ and for splenectomy.⁷ In the light of this knowledge, we decided to make a trial of this incision for the removal of large kidney tumors, and performed our first nephrectomy by this route in January, 1948. (Although Mortensen,⁸ of Australia, had removed a large tumor in this manner in June, 1946,

we were quite unaware of this, since his case report had not yet been published.)

The excellent exposure that was found to be afforded by this approach greatly facilitated nephrectomy in these difficult cases and led to much enthusiasm on our part, our first few cases being reported in May, 1948.⁹ Further experiences with the incision, which has now also been employed with success by several colleagues, have only served to increase our liking for it, and it has now been used in 39 cases for urologic surgery. Twenty of these operations were for renal tumors, and 12 were for the exploration or removal, or both, of kidneys suspected of tumor (mostly large solitary cysts). This procedure has also been utilized to allow nephrectomy when the usual approach to the kidney was blocked by the ribs owing to extreme kyphosis or scoliosis of the spine (2 cases). Furthermore, the particularly excellent exposure of the retroperitoneal region from the diaphragm down that can be obtained by this approach has led to its use, by extension of the incision downward toward the pubis, for retroperitoneal dissection of the lymph nodes along the aorta, vena cava and iliac vessels in cases of carcinoma of the testis (5 cases), and for complete nephroureterectomy in another case, in which the tumor of the renal pelvis involved the ureter. These other uses of the incision in urologic surgery are not discussed further, this communication being confined to a description of the experiences with this approach in the 20 cases of kidney tumor.

The discouragingly low incidence of five-year (15 to 19 per cent) and ten-year (7 to 9 per cent) cures^{10,11} of malignant kidney tumors is obviously due to their high degree of malignancy, coupled with the frequently insidious nature of their onset, especially the renal-cell carcinoma-hypernephroma cases which comprise the majority of these tumors. In this group the blood supply is very rich, and the malignant tissue is in intimate contact with the vascular spaces, and often parts of the tumor actually project into the blood stream. Thus it is that distant metastases from these tumors

*From the Massachusetts General Hospital.
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consulting general surgeon, Wills Hospital, Philadelphia. With a foreword by Joseph C. Yaskin, M.D., professor of neurology, University of Pennsylvania School of Medicine. Third edition. 8°, cloth, 357 pp., with 181 illustrations. Philadelphia: F. A. Davis Company, 1949. \$6.00.

This third edition of a special monograph, formerly called *Segmental Neuralgia in Painful Syndromes*, has been thoroughly revised, and material added on endometriosis as a cause of major backache, the intravenous use of procaine as a method of pain control, technique for aborting attacks of migraine and atypical facial pain. The chapter on brachial-plexus pain has been enlarged by the inclusion of a new summary of etiologic factors, a new outline of etiologic factors and a differential method of examination. The chapter on the anterior-scalene syndrome has been thoroughly revised. The book is well published and should be in all medical libraries and available to neurologists and physicians interested in the subject of pain.

The Venereal Diseases. A manual for practitioners and students. By James Marshall, M.D., M.R.C.S., L.R.C.P., director, Venereal Diseases Clinic, Royal Northern Hospital, London, and consulting dermatologist, Central Middlesex County Hospital. Second edition. 8°, cloth, 369 pp., with 105 illustrations. London: Macmillan and Company Limited, 1948. \$5.50.

In this second edition of a manual first published in 1944 the author has incorporated the use of penicillin, rewritten the sections on nongonococcal urethritis, brought up to date massive arsenotherapy, added a note on Reiter's syndrome and made many minor revisions and corrections. The book is well published, and there is a good index. The volume should prove valuable as a quick reference source.

Safeguarding Motherhood. By Sol T. DeLee, M.D., clinical instructor of obstetrics and gynecology, University of Illinois College of Medicine, and attending obstetrician at the Chicago Maternity Center. 8°, cloth, 135 pp., with 42 illustrations. Philadelphia: J. B. Lippincott Company, 1949. \$2.00.

This manual for expectant mothers has been written by an obstetrician. The chief purposes of the book are to inform them regarding their pregnant condition, the means whereby the body has been prepared for it, the course it will follow and the culmination in the birth of the child. It is to be used in co-operation with an obstetrician. There is a glossary of uncommon and technical words and phrases used in the text. There is a good index. The publishers have produced a beautiful book with excellent illustrations.

Etudes de pathologie foetale et néonatale. By Dr. M. Sorba. 8°, paper, 160 pp., with 14 illustrations. Lausanne: F. Rouge & Cie S.A., 1948.

In this monograph Dr. Sorba discusses the various aspects of fetal neonatal pathology. The text is divided into four parts: lesions of the fetal annexes and the fetus, interpretation of the lesions and syndromes, causes and mechanisms of death, and fetal and neonatal pathology. A bibliography concludes the text. A table of contents takes the place of an index. The monograph is well published and should prove of interest to persons interested in the subject.

Clinical Case-Taking. Guides for the study of patients. History-taking and physical examination or semiology of disease in the various systems. By George R. Herrmann, M.D., Ph.D., professor of medicine, University of Texas Medical Branch. Fourth edition. 8°, cloth, 240 pp. St. Louis: C. V. Mosby Company, 1949. \$3.50.

This manual was first published in 1927 and has been revised and brought up to date. It is intended for ward and bedside practice. The method of interviewing patients—to establish what sort of a human being each one is—has been added in the general outline for all cases, as well as in the section on psychiatry. The significance of personality functions as motivating factors in psychosomatic disorders has been pointed out. There are new sections on pediatrics and surgical case study. The table of contents has been arranged as a working outline, and there is a good index. The book is well published.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the Lower Outpatient Amphitheater, Massachusetts General Hospital, on Tuesday, December 13, at 8 p.m.

PROGRAM

Spatial Relationships of the Deep Veins of the Lower Extremity. Davitt A. Felder.
Venous Pressures in the Lower Extremity. Richard Warren.
Management of Late Phlebotic Sequelae. Irad B. Hardy, Jr.
Problems in the Management of Portal Hypertension. Robert R. Linton.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Thursday, December 15, at 8:15 p.m. A symposium on early diagnosis of cancer will be conducted, with Dr. Arnold M. Seligman as moderator. Dr. Monroe J. Schlesinger will discuss "Histopathologic Diagnosis," Dr. Olive Gates "Aspects of Cytologic Diagnosis," Dr. William Fishman "Biochemical and Enzymatic Diagnosis," and Dr. Freddy Homburger "Evaluation of Cancer Tests."

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A Tuesday evening lecture sponsored by the Boston City Hospital House Officers' Association will be presented in the Dowling Amphitheater, Boston City Hospital, on December 20 at 7 p.m. Dr. Ephraim Shorr of the New York Hospital and Cornell University Medical College will speak on the subject "The Role of Vasoactive Principles of Liver and Kidney Origin in Experimental Shock, Hypertension and Cirrhosis."

All interested physicians are invited to attend.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, December 14, at 8:00 p.m. Dr. Stanley J. Sarnoff will speak on the subject "Electrophrenic Respiration with Consideration of the Management of the Respirator Difficulties in Bulbar Poliomyelitis" (with motion pictures, slides and demonstrations of electrophrenic respirator techniques). This will be followed by a general discussion.

There will be a meeting of the Council at 7:30 after an informal dinner in the Empire Room at 6:00 p.m.

Physicians, physical therapists, occupational therapists and corrective therapists are cordially invited to attend this program.

ASSOCIATION OF SCHOOL PHYSICIANS OF MASSACHUSETTS

A dinner meeting of the Association of School Physicians of Massachusetts, which will also be a membership and organizational meeting, will be held at the Pocahontas Club, Lynnfield, on Wednesday, December 21, at 6:30 p.m. The speakers will be Dr. William E. Welch, superintendent of schools in Peabody, and president of the Association of School Superintendents of Massachusetts, and Dr. William M. Schmidt, associate professor of maternal and child health practice, Harvard School of Public Health, who will discuss his postwar experiences in Europe.

LABORATORY COURSES AT COMMUNICABLE DISEASE CENTER, ATLANTA, GEORGIA

A schedule of laboratory training courses will be offered at the Communicable Disease Center, Laboratory Division, Atlanta, Georgia, from January 9 to December 1, 1950. Application forms and further information regarding the subjects, duration and location of the various courses may be obtained from the Chief, Laboratory Division, Communicable Disease Center, 291 Peachtree Street, N.E., Atlanta, Georgia.

(Notices concluded on page xiii)

and often dangerous hemorrhage from the large veins that run over the surface of some of these large renal tumors. It is believed that these veins are often the result of venous stasis and engorgement secondary to obstruction of the renal vein by a tumor thrombus, and that this back pressure accounts for the fact that they bleed so profusely.

By this route, enlarged regional lymph nodes at the renal pedicle and along the vena cava and aorta were removed in 6 cases. In 4 of these, the removed lymph nodes showed malignant spread, but in 2 cases they surprisingly showed no disease. Two other patients had tumors projecting into the renal vein that were successfully removed. In another case the vena cava was opened and part of its wall excised to remove a tumor thrombus going down it for 1 cm and adherent inside it. In another case the vena cava, which was involved by direct extension from a malignant tumor of the right kidney, was ligated just below the left renal vein, and a section of it removed with the tumor. As yet, we have encountered no cases with direct extension to the diaphragm, spleen, duodenum or colon, but we believe that if this situation were encountered, resection of the involved portions of those structures might prove feasible. One tumor of the left kidney had already metastasized to the liver, and a tumor on the right had extended directly into the liver. In the latter case the porta of the liver was involved, and although the kidney was removed, it was believed that the disease in the liver was inoperable. However, if the direct extension had been to a more peripheral region of the liver, resection of the involved portion might have been possible. At the time of operation, 1 patient had already had his arm amputated for a metastasis to the humerus, and 2 patients were known to have pulmonary metastases. In view of the occasional cure of a patient with one solitary metastasis by its removal followed by the extirpation of the primary tumor,¹² the renal neoplasm of the first was removed in the vain hope of a chance of cure, and nephrectomy was performed on the latter 2 for the relief of hematuria and pain.

This incision has been performed on both sides, but somewhat more often on the left side than on the right. On the right, even with very large kidney tumors and with somewhat enlarged livers, the overhanging anterior edge of the liver has been easily retracted upward out of the way, and has not interfered with the performance of the operation.

Owing to the fact that the chest wound is held widely open by the rib retractor, less muscular relaxation is needed, and therefore less ether is used than when a comparable operation is performed through the abdominal musculature alone. This can be an important consideration in older and poor-risk patients.

The patients varied in age from one year (a baby boy with a large cystic teratoma) to seventy-seven

years, and 5 patients were over seventy. Two of these had severe cardiac conditions, compensated only on limited activity, and 3 others had electrocardiographic evidence of coronary sclerosis. Despite these limitations, with the exception of a woman of seventy-seven whose heart decompensated temporarily one week after operation, the postoperative recoveries were uneventful and the length of the postoperative hospital stay was the same as that for uncomplicated lumbar nephrectomies.

In these 20 thoracoabdominal operations for kidney tumor there has been no operative mortality or death in the hospital. Also, there have been no pulmonary emboli or cases of chest or peritoneal infection (These statements are also true for the total of 39 thoracoabdominal urologic operations performed to date.) There were only 2 significant postoperative complications, both of which were due to intrapleural hemorrhage. The first hemorrhage was minor, and the chest cleared after one thoracentesis. The second case continued to ooze intrapleurally, probably from torn pulmonary adhesions, and required several chest taps, as well as blood transfusions, during the first few days after operation. Eventually, the blood in the chest became so thick and clotted that it could not be removed, and it bound down and collapsed the lower and middle lobes of the right lung, making an open surgical decortication necessary. The patient, who was seventy-five years of age, tolerated this procedure well and went home in good condition. There were no other postoperative complications.

Thus, it can be seen that we, as well as our colleagues, have experienced a minimum of complications from the thoracoabdominal incision. We are firmly convinced that the important advantages that it confers through the wide exposure are well worth the added effort of the necessarily more complicated operative procedure and of the more exacting preoperative and immediate postoperative care. Also, whereas at first this approach was suggested only for kidney tumors that were obviously large, with further experiences and in view of the good possibility that local extension will be found at operation on any kidney tumor, it is our opinion that one must always be prepared for extensive surgery in every case with the best possible exposure, and that therefore all renal tumors should be operated upon by the thoracoabdominal route.

At the present time, the series of cases is too small and the length of follow-up study far too short to permit any true appraisal of end results, but the operative technic facilitated by this incision should improve the chances of cure and the end results. The patient who could not be operated on died within a few months, and the patient who had nephrectomy and amputation of the arm for what was hoped to be a solitary metastasis is now dying of widespread metastases to the spine, ribs and lungs. In addition, 6 patients, 2 of whom were

take place via the efferent blood vessels, such as the renal vein. Local lymphatic metastases to the regional lymph nodes, the nearest of which are located in the region of the renal pedicle and along the nearby anterior aspect of the aorta and vena cava, also occur. Therefore, it is not surprising that many patients die of metastatic disease despite removal of the primary tumor, sometimes succumbing even ten years after nephrectomy. A contributing unfavorable factor is the fact that the patient often is not operated on until the disease is in an advanced stage, either on account of the frequent absence of symptoms until late in the disease or because such symptoms as hematuria have been disregarded. It is indicative of the high malignancy and insidious onset of the tumors that at operation only 8 of the 20 patients in this series were found to have no evidence of extension of the disease outside the kidney, despite the fact that many had had symptoms for only a short time.

It also seems very probable that some of the late distant metastases that not infrequently follow the removal of malignant kidney tumors are due to the fact that particles of tumor have been literally squeezed into the blood stream by the manipulations of the operator while he is freeing up a large vascular tumor preparatory to its removal. Thus, ideally, the surgeon performing a nephrectomy in these cases should interrupt the connection of the kidney tumor with the systemic circulation by clamping the renal vein before he handles the tumor and massages malignant tumor emboli into the blood stream. In addition, such a nephrectomy, to be an adequate operation for cancer in accordance with modern concepts of cancer surgery, should also remove — en bloc with the tumor, if possible — regional lymph nodes and also all the perinephric fat and capsule of Gerota, if possible. Such a procedure is analogous to the dissection of the axillary lymph nodes en bloc with the breast in a radical mastectomy for carcinoma. The ability to perform this type of nephrectomy, which, in our opinion, may prove to be an important step in improving the results of the surgery of these malignant tumors, very largely depends on an exposure wide enough to facilitate its easy and safe performance.

The thoracoabdominal incision furnishes the wide exposure needed. It neutralizes the barrier of the bony thoracic cage, inside which the kidney largely lies, by means of creating surgically a broad pathway directly through it right to the kidney. This gives an exposure of this organ and its pedicle that is direct and wide and definitely superior to that afforded by either the lumbar or the transperitoneal approach in our opinion and that of our colleagues who have used it.

When malignant renal tumors are large, and especially when there are involved lymph nodes adherent to the great vessels in the region of the pedicle or when there is invasion of the inferior

vena cava by tumor thrombi, their removal may be exceedingly difficult and dangerous, and sometimes impossible. In such difficult cases the difference between success or failure may depend on whether or not there is good exposure and room to carry out delicate and exacting surgical procedures. As a result of the wide-open approach conferred by the thoracoabdominal incision, both the ease and the safety of the removal of renal neoplasms have been greatly increased, since, even with the largest tumors encountered, the vessels of the pedicle have been fairly easily discovered, and exposed and ligated individually under direct vision. This has decreased the liability to such accidents as uncontrollable hemorrhage and injury to the vena cava, spleen, colon or duodenum, which have sometimes occurred in the past, usually when the surgeon was working in cramped quarters in a deep wound with inadequate exposure and imperfect visualization of important structures. In such cases a lumbar or transperitoneal incision had often been made as long as it was possible to make it, but limitations inherent in the type of incision had resulted in an exposure that was still inadequate for the condition the surgeon was contending with. Those who have operated upon these large vascular tumors under such difficult and unpleasant circumstances will easily appreciate the great value of an exposure that affords both plenty of room and good vision.

As a corollary, it is not surprising that this exposure has allowed the extirpation of large carcinomatous kidneys whose removal had been attempted by another approach but found impossible. In one of our cases a large tumor, whose removal had been attempted unsuccessfully via the lumbar approach by an experienced urologic surgeon, was taken out successfully ten days later via the thoracoabdominal route. The case reported by Mortensen⁹ had also been attempted unsuccessfully by the conventional route. In another of our cases in which the thoracoabdominal approach was successfully employed, a huge kidney was found to be very adherent to the vena cava for a distance of about 5 cm. and had to be dissected off with great care; it seems quite certain that the kidney could not have been removed by any other approach without serious damage to the vena cava. Several other tumors in our series probably could not have been removed successfully through any other incision. In this connection, it is significant that in only 1 of these 20 neoplasms, some of which were very large and adherent with local extension, was the kidney not removed. In this case widespread local extension of the malignant lesion seemed to contraindicate any attempt at nephrectomy.

Another technical advantage conferred by this wide-open exposure is that, by facilitating the early ligation of the vessels of the renal pedicle before very much manipulation or freeing-up of the kidney is necessary, it largely avoids the bothersome

portant to resect the rib as far back toward the spine as this because, if it is resected farther forward, the ligaments binding it to the rib above and the rib below will prevent the optimum spread of

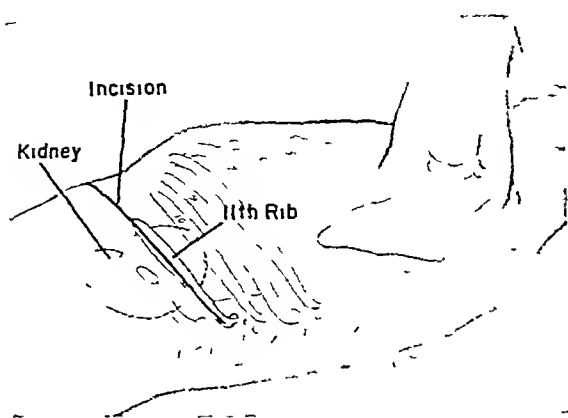


FIGURE 2 Schematic Drawing, Showing the Location of the Incision in Relation to the Kidney

this posterior angle of the wound, which is essential to the maximum possible exposure from this incision. The pleural cavity is entered through the periosteal bed, great care being taken not to injure the underlying lung (Fig 4). There is less

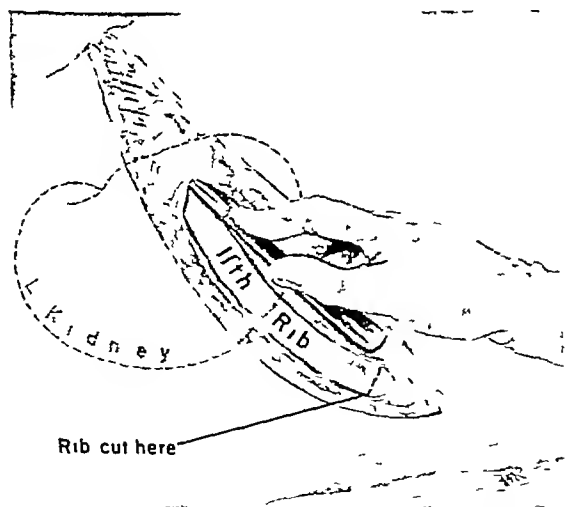


FIGURE 3 Drawing Showing the Incision for Left Nephrectomy, Starting from Near the Spine in Back Running Forward and Downward over the Left Eleventh Rib and Continuing to the Outer Border of the Left Rectus Muscle
The rib is being cleared preparatory to subperiosteal resection

chance of doing this if the pleural cavity is opened anteriorly over the diaphragm. The anesthetist is notified when the pleural cavity is entered. Unless adhesions are present, the lung collapses consider-

ably on opening of the pleural cavity and retracts upward. If adhesions between the lung and the parietal pleura or the diaphragm are obvious and in the way, they are gently separated by sharp dissection, great care being taken to secure complete hemostasis with fine-silk ties or ligatures. During the operation the lung can be walled off by moist gauze and the anesthetist may keep it almost completely expanded. By retracting the chest wall up and the diaphragm down, one can see the phrenic nerve as it courses downward over the pericardium, and it may be crushed with a hemostat at the point where it leaves the surface of the pericardium to enter the diaphragm. This paralyzes the diaphragm and stops its motion, so that it interferes less with

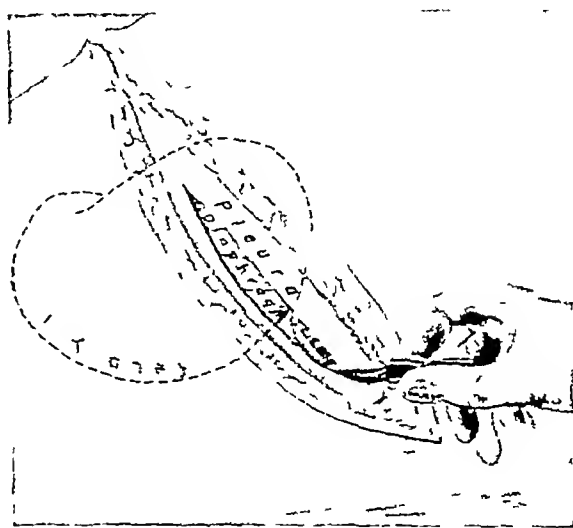


FIGURE 4 Drawing Showing the Left Pleural Cavity Being Entered through the Periosteal Bed of the Left Eleventh Rib
Care is taken not to wound the underlying lung

the operation. The paralysis lasts for about four to six weeks, and the resulting immobility is thought to aid the healing of the diaphragm. However, if the patient has a low vital capacity and it is desirable for him to have the positive muscular action of the diaphragm return soon to help him with respiration, the phrenic nerve is simply injected with a few cubic centimeters of 2 per cent procaine solution, which allows its action to return in an hour or two, and this precaution ensures better postoperative aeration of the lung above. In some cases the phrenic nerve has not been touched, and the motion of the diaphragm has not seemed to interfere with the renal surgery. The diaphragm is then incised in line with the skin incision, the incision also being carried through the peritoneum which is adherent to its undersurface. Care is taken to avoid cutting into any organ that may be adherent to its underside, such as the kidney tumor, or the

known to have pulmonary metastases before operation, have demonstrable metastases to which they will eventually succumb. The other patients are living and apparently well.

The following cases illustrate the problems that occur and show why all renal tumors should be operated upon by the route giving the best possible exposure.

CASE REPORTS

CASE 1 A 59-year-old man, previously in excellent health, noticed bloody urine for the first time in his life and had colicky pains from passing clots. After 10 days of this he entered the hospital, where the diagnosis of a tumor of the right kidney was made after x-ray study, even though no mass could be felt. He was operated upon by the lumbar route, and the tumor was found to be so large, to lie so high and to be covered by large veins that bled so profusely that, after a prolonged attempt to free it up, it was considered inoperable and the wound closed. Eleven days later, on account of continuing intractable hemorrhage and colic, the kidney was approached by the thoracoabdominal route and easily exposed. It was found that there was a tumor thrombus about 1.5 cm in diameter filling the renal vein and extending retrograde downward inside the vena cava for 1 cm. After temporary tension tapes had been applied to the vena cava above and below to control bleeding, the vena cava was opened and it was found that the tumor thrombus had invaded the wall of the vena cava near the entry of the renal vein. The involved portion of the wall of the vena cava was excised and removed with the thrombus and renal vein, after which the kidney was easily removed. The incision in the vena cava was sutured longitudinally with fine silk, and the patient made a very satisfactory recovery. So far he has remained in excellent health for the 4 months since his operation. The microscopic diagnosis was renal-cell carcinoma.

CASE 2 A frail, 77-year-old woman with a poor heart entered the hospital with a 3 weeks' history of colicky pain in the right-kidney region associated with episodes of hematuria. She had lost weight, felt tired and had dyspnea on exertion. Examination showed her to be extremely anemic. A large hard mass, which did not move much, was felt in the right-kidney region. After the anemia had been remedied by multiple transfusions, the patient was operated upon through a thoracoabdominal incision. A huge kidney was found adherent to the liver and the duodenum. It was dissected off these structures, but then it was found that the tumor intimately involved much of the circumference of the vena cava. Since this was below the entrance of the left renal vein, the vena cava was tied off here, and a segment of vena cava removed with the tumor, as well as some involved nodes. After a somewhat stormy convalescence, marked by oliguria for some days and also by cardiac decompensation, the patient made a satisfactory recovery. The microscopic report was squamous-cell carcinoma.

CASE 3 A 67-year-old man had had cardiac decompensation 3 years previously. After several weeks of bed rest and digitalization he recovered enough cardiac compensation and reserve to be able to get along fairly well on limited activity. For 6 months he had noted an occasional streak of blood in the urine, and 3 days before admission he had noticed definitely bloody urine, with some aching in the left flank. Examination showed a moderate-sized, rather fixed mass high up in the left upper quadrant, and pyelograms indicated a good-sized tumor of the left kidney. After a few days of cardiac preparation with digitals, a low-salt diet and quimidine immediately before operation, thoracoabdominal nephrectomy was carried out. A large renal tumor was found, and after preliminary ligation of the renal vein and artery, an egg-sized mass of metastatic lymph nodes in continuity

with the lower pole of the kidney and extending downward along the anterior surface of the aorta was gently dissected free and removed en bloc with the kidney (Fig 1). The patient made an uneventful recovery, having no cardiac embarrassment, and when last examined and given x-ray study



FIGURE 1 *Kidney Tumor, with Attached Metastatic Nodes Removed en Bloc (Note That All the Surrounding Fatty Capsule Is Removed with the Kidney)*

14 months later was well, with no evidence of metastases. Microscopic examination revealed renal-cell carcinoma with extension to the lymph nodes.

OPERATIVE TECHNIC

In preparation for the operation of thoracoabdominal nephrectomy, particular attention is paid to increasing the hemoglobin and red-cell count to normal. Older patients and all who have cardiac abnormalities are seen by a cardiologist, and most of these are put on a low-salt diet, some are digitalized, and almost all are given quimidine preoperatively. If the nephrectomy is to be on the left side, a Levine tube is placed in the stomach immediately before operation, to prevent gastric distention, which can be troublesome in operations on that side.

Under intratracheal oxygen-ether anesthesia, the patient is placed on the operating table with the side to be operated upon uppermost. The incision starts about 1 cm lateral to the spinous processes of the spine in back and runs forward and downward over the entire course of the tenth (or eleventh) rib (Fig 2). When the end of the rib is reached, the incision is continued in the same direction across the abdominal wall as far as the lateral border of the rectus muscle. The incision is deepened through the muscle layers to the rib, which is removed in its entirety subperiosteally, being resected between its posterior angle and the spine (Fig 3). It is im-

main renal artery is exposed, the vein and the artery are individually clamped, sectioned and doubly ligated — as well as any smaller vessels found

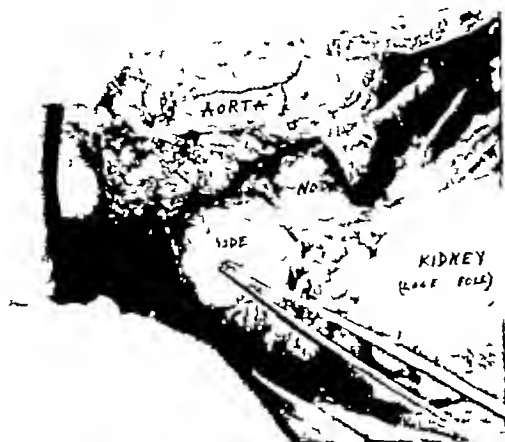


FIGURE 9 Photograph Taken at Operation Showing Metastatic Lymph Nodes Dissected from the Aorta en Bloc with the Kidney

In addition to the perinephric fat, all lymph nodes and areolar tissue in the region of the pedicle or adherent to the great vessels are dissected away —

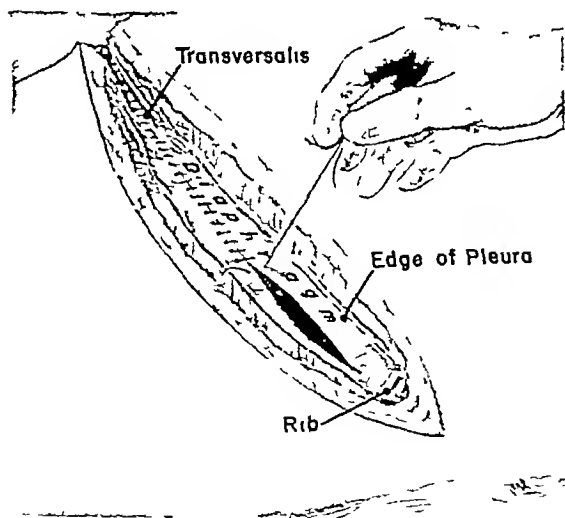


FIGURE 10 Drawing Showing Wound Closure

The anterior part of the peritoneum, from the outer border of the rectus muscle to the diaphragm, has already been closed. The drawing shows the suturing, with interrupted silk stitches, of the diaphragm and of the transversalis muscle, with which it decussates to form a continuous muscle layer for the purposes of closure

being removed en bloc with the tumor, if possible (Fig 9) The ureter is sectioned and ligated, the cut ends being carbolyzed After this, it is a simple

matter to complete the mobilization of the kidney and remove it If there is direct extension to some neighboring structure such as the diaphragm, it is quite possible that enough of this structure can also be excised to eradicate this extension of the malignant process After the kidney has been removed, a few stitches may be taken to cover the raw area with peritoneum and to fix the bowel back in position Then the opening in the peritoneum is closed anteriorly as far back as the diaphragm, a continuous suture of plain O catgut on an atraumatic needle being used When the diaphragm is reached, it is sutured with interrupted stitches of heavy silk (No 2) (Fig 10) Before the chest is closed, 15 cc of eucupine in oil (a long-lasting local anesthetic) is injected hypodermically into the intercostal nerve of the rib resected, and also into the nerve of

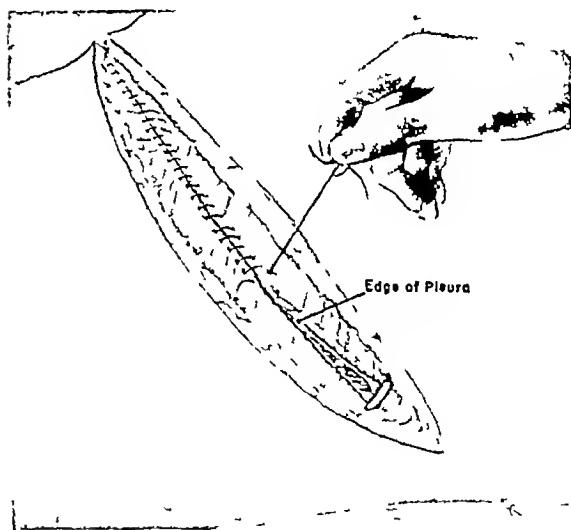


FIGURE 11 Drawing Showing Closure of the Pleura and of the Muscles in Layers with Interrupted Silk Sutures

the rib above and below This is done inside the chest behind the angle of each rib It tends to prevent postoperative neuritic pain in the area of the operation, and thus also helps to reduce voluntary "splinting" of the chest after operation with decrease of respiratory exchange The pleura is re-approximated with interrupted silk sutures The last two sutures are placed but not tied until the lung has been completely re-expanded by the anesthetist The muscles are closed in layers with interrupted sutures of No 3 silk throughout, and the skin is closed with silk (Fig 11) An alternative method of closing the pleural cavity is to place a No 18 catheter in the pleural cavity and close the pleura and wound about it, bringing the catheter out in a slanting manner When the wound is all sutured except the skin, the anesthetist re-expands

liver on the right side, and the spleen or colon on the left side (Fig 5) The incision in the diaphragm is carried forward through the decussation of the diaphragm with the transversus abdominis muscle

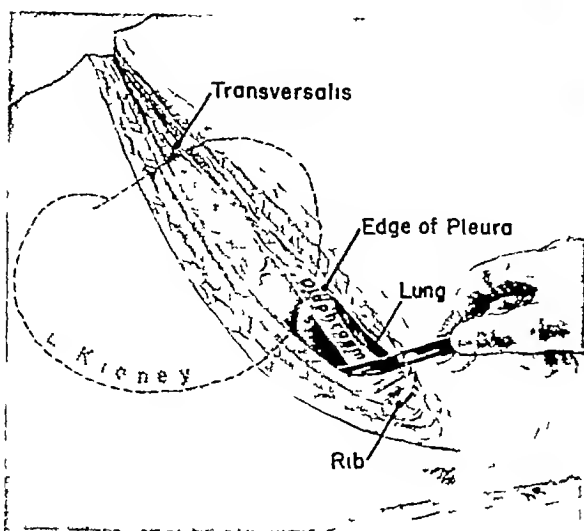


FIGURE 5 Incision through the Diaphragm and Underlying Peritoneum Carried Forward through the Transversalis and Oblique Muscles to the Outer Border of the Left Rectus Muscle Care is taken not to injure underlying organs, such as the spleen, kidney and colon

and, of course, through the oblique muscles as far as the outer border of the rectus muscle, thus opening the peritoneal cavity widely (Fig 6) A Finochietto rib retractor is used to separate the ribs,

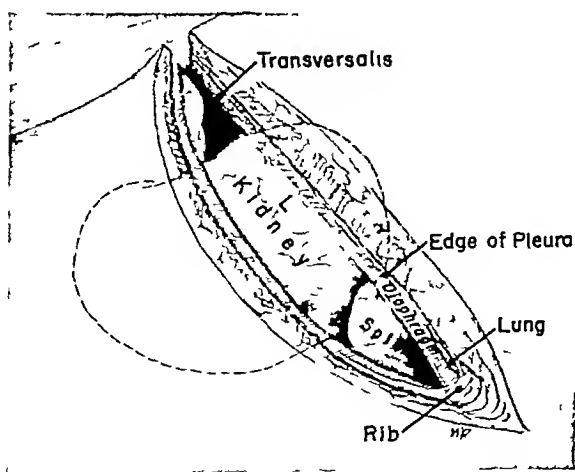


FIGURE 6 Drawing Showing the Peritoneal Cavity Widely Opened

and the kidney then bulges up into the wound (Fig 7) On the right side the liver also presents, but even if it is somewhat enlarged, it is easily retracted upward out of the way On the left side the

spleen presents and, if it is in the way, it is packed off upward The renal tumor, surrounded by its intact fatty capsule, is gently retracted laterally, the

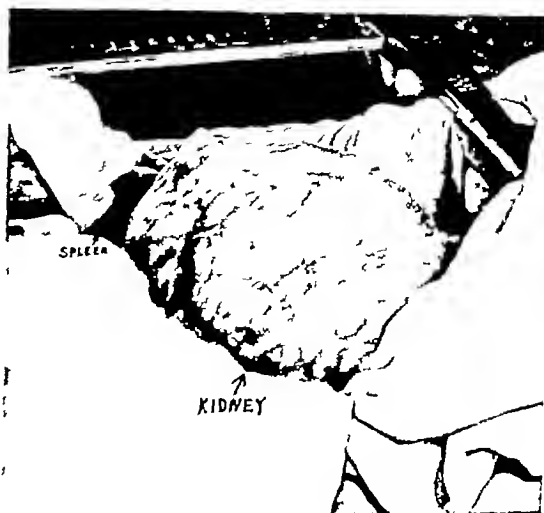


FIGURE 7 Photograph Taken at Operation, Showing the Wound Spread Widely with a Rib Retractor, and the Tumor of the Left Kidney Bulging up into the Wound of Its Own Accord As yet it has not been freed up at all The spleen is packed away above

duodenum or colon, according to whether the operation is on the right or left side, is gently and carefully freed from its medial aspect, and the renal

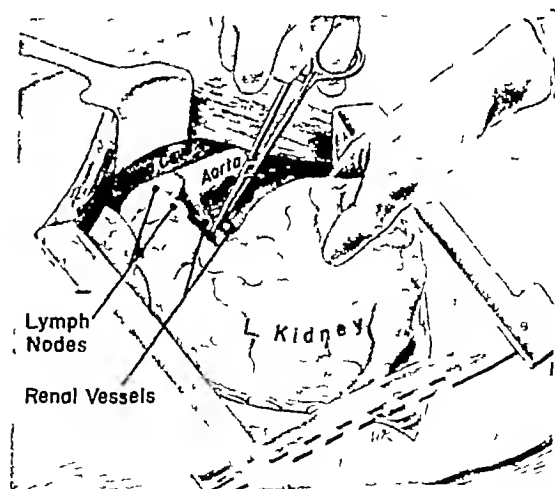


FIGURE 8 Drawing Showing the Tumor Being Gently Retracted Laterally and the Colon Easily Separated from Its Anterior Medial Surface

The vessels of the renal pedicle are secured individually under full vision Metastatic lymph nodes along the aorta will be removed with the kidney

vein is easily exposed and may be dissected out cleanly (Fig 8) The dissection of the pedicle is then continued under direct vision, and when the

at 8 cm. of negative pressure for forty-eight hours. Thereafter, if there is no further indication for its use, it is removed and the wound immediately covered with a vaseline-gauze dressing to prevent an air leak. A transfusion of 1000 cc. of whole blood is given at the time of the operation. Thereafter, blood is given only as indicated, and is usually not necessary.

The technic on the right side is similar (Fig 12-15).

Postoperatively, the patient is managed as a chest case. The quinidine and penicillin, with digitalis, if necessary, are continued. Streptomycin in addition may be necessary if the type of bacterial contamination from the kidney warrants it. The patient is turned every hour from his operative side to his back to help avoid atelectasis. Oxygen is given by nasal catheter until there is good aeration of both lungs. This may be for several days, but is usually only for twelve to twenty-four hours.



FIGURE 16 Photograph Showing the Healed Wound Ten Days after Operation

This method provides a fair concentration without interfering with the care of the patient as a tent does, or bothering him as a mask does. The Levine tube is attached to suction for a day or two. Morphine should be administered early and frequently, particularly in patients with coronary-artery disease, for by lessening pain it aids depth of respiration, and diminishes the combination of pain and anoxia that leads to undue restlessness postoperatively and may favor coronary occlusion. Care must be taken to give it in amounts that will not depress the respiratory rate unduly. Intravenous administration of fluids is performed slowly without saline solution (except when such a solution is specifically indicated) unless the patient is young and his cardiac status is good. The patient is allowed up usually on the first postoperative day, and is ready to go home in about ten days as a rule (Fig 16).

SUMMARY

The thoracoabdominal approach has been used in 39 cases for urologic operations—in 20 for kidney tumors (19 nephrectomies) and in 12 for

the exploration or removal, or both, of kidneys that were suspected of being malignant but turned out to be benign (usually large solitary cysts). In 2 cases it has been utilized to allow nephrectomy when the usual approach to the kidney was blocked by the ribs in kyphosis or scoliosis of the spine. In addition, by extending the lower end of the incision downward toward the pubis, it has been used for retroperitoneal dissection of the lymph nodes in the region of the kidney pedicle and along the aorta, vena cava and iliac vessels in 5 cases of carcinoma of the testis, and for complete nephroureterectomy in 1 case in which the tumor of the renal pelvis involved the ureter.

The experience with this incision in the surgery of 20 cases of renal tumor is discussed.

It is our opinion and that of our colleagues that the thoracoabdominal incision affords a much wider and better exposure of the kidney and its vascular pedicle than the extraperitoneal lumbar or the transperitoneal approach.

This wide-open exposure confers the following advantages: greater ease and safety in securing the vessels of the renal pedicle, less manipulation of the kidney before the renal vessels are secured, thereby minimizing the probability of squeezing malignant tumor emboli into the blood stream, increased ability to remove all the perinephric fat and capsule of Gerota with the kidney, increased ability to remove large and extensive kidney tumors, some of which have been found inoperable by another approach, increased ability to remove the malignant extension of renal tumors to the inferior vena cava or to regional lymph nodes, thus constituting a more adequate operation for cancer (such extensions were removed en bloc with the kidney in several cases), and, by early ligation of the renal vascular pedicle, elimination to a large extent of the bothersome and often dangerous hemorrhage from large veins that run over the surface of some kidney tumors.

Because the chest wound is held widely open by the rib retractor, less muscular relaxation is needed, and therefore less ether is used than when a comparable operation is performed through the abdominal musculature alone.

In these 20 thoracoabdominal operations for kidney tumor there has been no operative mortality or death in the hospital. Also, there have been no pulmonary emboli or cases of chest or peritoneal infection. (These statements are also true for the total of 39 thoracoabdominal urologic operations performed to date.) There have been only 2 complications, both of which were due to intrapleural hemorrhage. The first was minor, requiring only one thoracentesis, but the second was major, requiring several paracenteses for the removal of blood, as well as transfusions, and eventually a surgical decortication of the lung. The patient made a satisfactory recovery.

the lung with positive pressure, suction is applied to the catheter to empty the pleural cavity, and then the catheter is withdrawn. Great care is taken not to prick the lung with the needle while the pleural

pleural cavity. If there is any doubt, it is always wiser to drain. Drainage is achieved by means of a No. 22 Foley catheter with a 30-cc bag in-

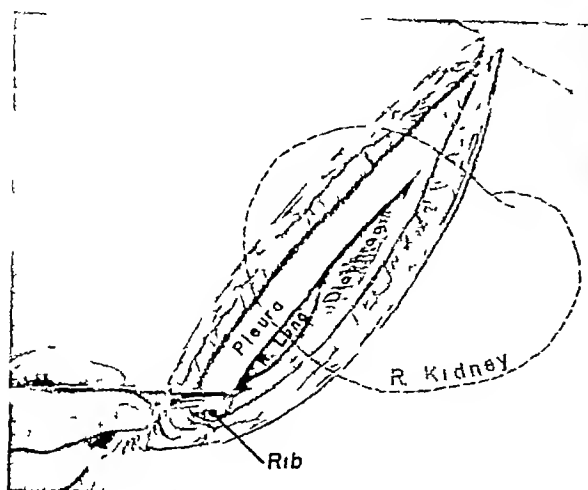


FIGURE 12 Drawing Showing a Similar Technic on the Right Side

The tenth or eleventh right rib has been removed, and the pleura is entered through the bed of the rib, care being taken not to injure the lung underneath

cavity is being closed. If this should happen, the edges of the wound should be carefully approximated with a fine atraumatic needle and suture

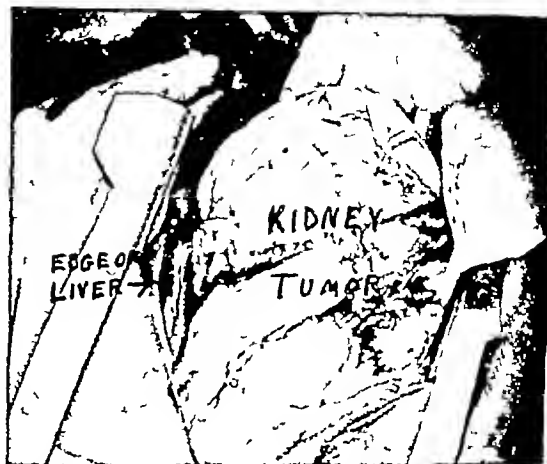


FIGURE 14 Photograph Taken at Operation, Showing the Tumor of the Right Kidney Presenting of Its Own Accord. As yet it has not been freed up at all. The liver is easily retracted upward out of the way

serted through a tiny stab wound in the chest wall two interspaces above the incision, in the axillary line. The catheter should not be led out through the main incision, since this interferes with healing. Its bag is inflated, and the catheter is

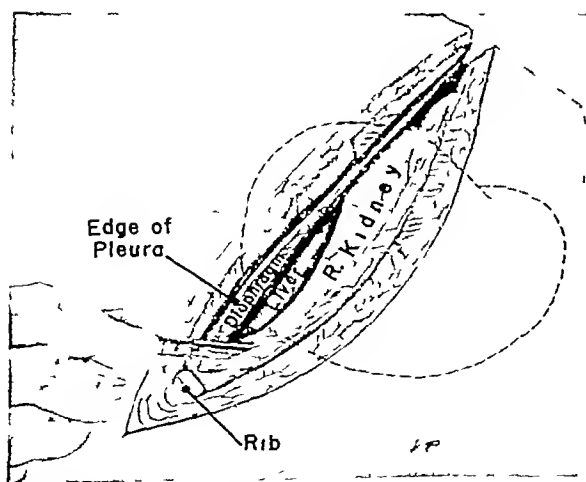


FIGURE 15 Drawing Showing the Incision of the Diaphragm and Underlying Peritoneum, Care Being Taken Not to Injure the Underlying Liver or Kidney

However, if the lung still leaks air on the application of positive pressure by the anesthetist, the chest must be drained. This must also be done when there is persistent oozing of blood into the

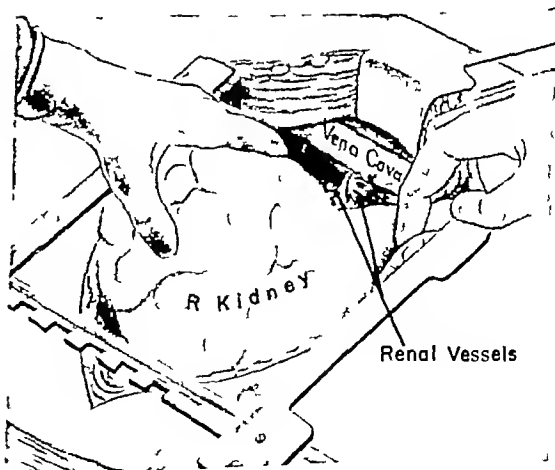


FIGURE 15 Drawing Showing the Tumor of the Right Kidney Being Gently Retracted Laterally, and the Duodenum Easily Separated from Its Anterior Medial Surface

The vessels of the renal pedicle are secured individually under full vision. The liver is easily retracted upward out of the way

tied off and brought against the chest wall. It is secured by a skin stitch as well. The chest catheter is connected to three-bottle chest-suction drainage

METHOD OF STUDY

The majority of the 77 women had prenatal care in the obstetric clinic or were delivered in this hospital. Eleven of them, however, had been attended and delivered by private physicians or had had no prenatal care and were delivered at home.

Detailed information regarding the maternal syphilitic infection was obtained in an interview with the patient, with special emphasis on the duration of the maternal infection, the results of all the patient's serologic tests and the amount of treatment received during and previous to pregnancy. Data regarding syphilitic infection in marital partners and other children were elicited whenever possible. Supplementary data were obtained from the hospital records, the city or county venereal-disease clinics, the State serologic laboratories and the patients' private physicians.

The diagnosis of congenital syphilis in the infants was based upon clinical findings, repeated quantitative serologic tests for syphilis, spinal-fluid studies, dark-field examinations and roentgenographic examination of the long bones. Approximately 80 per cent of the children showed what we consider to be definite roentgenographic evidence of osseous syphilis—that is, osteochondritis of the medial upper portion of the tibia, osteomyelitis and epiphysitis.⁴ Considerable care was taken in the interpretation of the serologic tests. No infant with latent syphilis was included in this study unless the serologic tests were found to be persistently positive in high titer. Almost all the patients in the group were infected before birth, since most of them showed overt manifestations of syphilis either at the time of delivery or very early in the neonatal period. Some of them, however, may have acquired syphilis by contact with infectious lesions at the time of delivery or in the early neonatal period.

NEGATIVE SEROLOGIC TESTS FOR SYPHILIS IN PREGNANCY

Several of the earlier studies on prenatal syphilis have shown that women with negative serologic tests in pregnancy may bear syphilitic children.² The low sensitivity of serologic tests was thought to be the cause of the negative serologic reaction in most of these patients, particularly in those with long-standing infections and previous therapy. With the increased sensitivity of serologic tests in recent years, such cases have become infrequent, and most workers now believe that women with persistently negative serologic tests will not bear syphilitic children.

Twenty-one patients in this study were known to have a negative serologic test in pregnancy and nevertheless delivered syphilitic children. In only 3 of these 21 patients was insensitivity of the Kahn and Kolmer tests considered to be the cause

of a negative reaction. These 3 women had a history of previous therapy for syphilis, and all of them continued to show negative, doubtful or very low titers in the absence of further treatment. The remaining 18 patients with negative serologic reactions in pregnancy demonstrated high serologic titers by the time of delivery or one or two weeks post partum. We believe that these 18 patients either were in the incubation period of the disease at the time of the negative test or acquired an initial or recurrent syphilitic infection later in pregnancy. Cutaneous manifestations of early syphilis were found in 5 of them at delivery or immediately post partum. Six of the 18 patients had been treated for syphilis prior to conception. Thus, a third of the patients in this series in whom syphilis developed during pregnancy had either a reinfection or a relapse of a previous infection, the remaining two thirds having contracted syphilis for the first time. The possibility that a technical error was the cause of negative serologic tests in pregnancy in these 18 patients is considered unlikely, since almost all of them gave a history of having had other negative serologic tests prior to conception. Moreover, the reactions to both Kolmer and Kahn tests were negative during pregnancy in 14 of the 18 patients.

The presence of active syphilis in the patients with negative serologic tests in pregnancy was not suspected, and no treatment was given before delivery. The diagnosis was made when a routine serologic test was obtained during labor or when the infection was suspected in the child. The lesions of early syphilis did not appear during pregnancy or were so inconspicuous as to have been overlooked by both the patient and the attending physician. Although pregnancy is generally believed to suppress the early lesions of syphilis, it does not produce a reduction in the titer of serologic tests or cause false-negative reactions.⁵ The diagnosis of syphilis in pregnancy could have been made in almost all these women if repeated serologic tests had been taken throughout the period of gestation. Only 2 women had a negative serologic test for syphilis at the time of parturition, both showed a high serologic titer within three months of delivery. The children of these 2 patients may have acquired syphilis before delivery during the incubation period of the maternal infection, or they may have been infected post partum. These children were not found to have syphilis until five to seven months of age, when they showed roentgenographic evidence of periostitis of the long bones.

The fact that clinic patients often acquire syphilis during the late stages of pregnancy has been noted by Beerman⁶ and Goodwin and Farber.⁷ These workers have emphasized the importance of repeating serologic tests during the last months of gestation to detect the presence of syphilis acquired

The patients varied in age from one year to seventy-seven years, and 5 patients were over seventy. The cardiac status of several of the patients was not good, and yet the postoperative recoveries were excellent, with the exception of a woman of seventy-seven who had temporary cardiac decompensation one week after operation.

Three case reports are presented.

This series is too small, and the length of follow-up study far too short to permit any true appraisal of end results, but the operative technic facilitated by this incision should improve the chances of cure and the end results.

On account of the excellent operative results with a minimum of complications and the frequency and unpredictability of local extension of malignant lesions of the kidney, the thoracoabdominal incision is recommended for all kidney tumors. We are firmly convinced that the important advantages that it confers are well worth the added effort of the necessarily more complicated operative procedure and of the more exacting preoperative and immediate postoperative care.

The technic of the operation and the preoperative and postoperative care are described.

We are indebted to Dr. Fletcher H. Colby for his encouragement in this work, and to him and to Drs. Wyland F. Leadbetter and George Gilbert Smith for permission to include some of their cases in this series.

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SYPHILIS IN PREGNANCY*

A Clinical Study of Factors Responsible for Congenital Syphilis

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THE incidence of infantile congenital syphilis has decreased considerably in the United States during the past two decades, nevertheless, cases continue to appear in significant numbers in most city hospitals.¹ Approximately 77 living infants with congenital syphilis have been treated at Grady Memorial Hospital in the past four years. Since congenital syphilis is preventable, it is necessary to inquire into the reasons for its continued occurrence.

Although several articles on factors influencing the outcome of syphilis in pregnancy have been published, the criteria for diagnosis of infantile congenital syphilis in many of these studies are no longer accepted. Thus, in the largest study reported that of the Clinical Cooperative Group,² the "information regarding transmission of syphilis to the child was limited to that obtained at birth." Similarly, in the study by Gammeltoft,³ a diag-

nosis of congenital syphilis was made when the "child as well as its mother gave a positive reaction, even in the absence of an eruption." Since the serologic test of both the umbilical-cord blood and that obtained in the neonatal period has been shown to have a limited diagnostic value, the accuracy of conclusions concerning the factors responsible for congenital syphilis in these studies is open to question.

Not only has the sensitivity and specificity of serologic tests for syphilis improved since the publication of these papers, but also many of the roentgenographic criteria for the diagnosis of congenital syphilis have undergone considerable modification. The presence of bismuth deposits or nutritional changes in the long bones, for example, was frequently misinterpreted as congenital syphilis.

For these reasons a reconsideration of factors responsible for congenital syphilis seems advisable. This paper presents a review of the syphilitic infection and therapy of the 77 mothers of the infants with congenital syphilis who were treated at the Grady Memorial Hospital in the past four years.

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during pregnancy can probably be withheld with safety *provided* one can be absolutely certain that a positive serologic test in pregnancy represents seroresistance of an infection that has been adequately treated and not a recurrent syphilitic infection. This differentiation is often very difficult. Many workers attempt to differentiate on the basis of the height of the serologic titer, but this is not always helpful, since a low titer does not always indicate seroresistance and a high titer does not necessarily mean a recurrent infection. Complete data regarding the syphilitic infection are necessary, and information should be obtained regarding not only the amount and type of therapy received but also the duration of the syphilitic infection before treatment, the status of the patient's marital partner and children, and the changes in serologic tests before conception and during pregnancy. If any doubt exists about the interpretation of these data, retreatment during pregnancy should be instituted.

TREATMENT DURING PREGNANCY AND OUTCOME OF PREGNANCY

A minimal amount of arsenical therapy given during pregnancy has been claimed to be effective in the prevention of congenital syphilis. McKelvey and Turner⁹ have reported that the administration of 12 to 14 injections of an arsphenamine to syphilitic women during pregnancy resulted in noninfected infants in 100 per cent of their cases. It was with some surprise, therefore, that we found that several of our patients had delivered syphilitic children, even though they had received as many as 20 injections of arsenoxide (Mapharsen) in pregnancy. Half, or 16, of the 32 women who were treated in pregnancy had 11 or more injections of Mapharsen, 9 of these had 16 to 20 injections. Only one of these 16 patients, however, began treatment before the fifth month. This patient had 9 injections of Mapharsen early in pregnancy, became delinquent for ten weeks during the sixth to the eighth month, and then received 11 more injections in the last five weeks of pregnancy. It should be emphasized, therefore, that although 10 to 20 injections of arsenoxide are often sufficient to protect the fetus of a syphilitic woman, this amount is not always adequate, particularly when given in the last half of pregnancy. The number of syphilitic children in this series born of mothers who had had what is generally considered "adequate" arsenical therapy in pregnancy is further evidence that this form of treatment should be replaced by penicillin.

Most workers now believe penicillin to be the drug of choice in prenatal syphilis. This form of therapy is not only more effective than arsenicals but also relatively nontoxic and can be given in a short period. Furthermore, it is valuable during the last trimester of pregnancy, a time when arsenical therapy is least useful. Penicillin has been shown

to be effective in the last few days of gestation, even when the child is already infected. We have observed a case in which delivery occurred on the seventh day of penicillin therapy after the patient had received 4,000,000 units of the drug in aqueous solution.¹⁰ The infant had a strongly positive serologic test and showed definite evidence of osseous syphilis by roentgenographic examination. The lesions of the long bones healed spontaneously, and the Kahn titer became and remained negative without further therapy, indicating that the child had received sufficient penicillin before birth for the infection to be cured. Similar cases have been reported elsewhere.¹¹ It must be emphasized, however, that penicillin is not uniformly successful for patients treated late in pregnancy. We have observed 2 patients, not included in this series, who were treated in the last trimester and delivered syphilitic, stillborn infants immediately after penicillin therapy. Death of the fetus was apparently caused by an overwhelming syphilitic infection.

In the present study only 1 patient who had completed the course of penicillin therapy during pregnancy delivered a syphilitic child. This patient received 4,800,000 units of crystalline penicillin G in aqueous solution during the fourth month of pregnancy. At that time the serologic test was positive with 40 Kahn units, and she had secondary syphilis. The Kahn titer fell to 4 units three weeks before parturition, but rose to 40 units two days before the syphilitic child was born, and before retreatment could be instituted. A recurrence of the maternal infection prior to delivery, as in this case, is one of the causes of congenital syphilis in infants born after penicillin therapy. Although it is infrequent, such a possibility should be kept in mind. Serologic tests should be taken at monthly intervals throughout pregnancy, and possibly more frequently near term. Retreatment with penicillin should be given during pregnancy if there is any doubt of the possibility of infectious or serologic relapse.

DISCUSSION

This study was stimulated by an attempt to determine the reasons for the large number of syphilitic infants delivered in or referred to this hospital. The presence of negative serologic tests in pregnancy and the inadequacy of arsenical therapy were responsible for the infection in two thirds of these infants. A number of other factors are believed to be of great importance in the transmission of congenital syphilis. Foremost among these is the failure of clinic patients to come for prenatal care early in pregnancy. One fourth of the 77 patients in this series did not receive any treatment during pregnancy because they came to the hospital just prior to or after the beginning of labor. Still others received inadequate therapy because they sought prenatal care late in pregnancy.

late in pregnancy. This practice, however, has not been a routine procedure in Grady Memorial Hospital. If followed, it should have permitted prevention of syphilitic infection in approximately 20 per cent of the children in our series. Although the need for repeating negative serologic tests in pregnancy is generally recognized, many physicians believe the procedure to be impractical, especially in large obstetric clinics. Repeated tests, particularly in the last eight weeks of gestation, are absolutely necessary, however, if the incidence of congenital infection among a clinic population with a high rate of syphilis is to be reduced to a minimum.

DURATION OF MATERNAL SYPHILIS AND OUTCOME OF PREGNANCY

It has been observed that women with early syphilis are more likely to bear syphilitic children than those with late syphilis. Nevertheless, there are numerous reports of transmission of congenital syphilis as long as ten to twenty years after the mother acquired the disease. Although most of these reports are not well authenticated, conservative opinion holds that antisyphilitic therapy should be given during each pregnancy, regardless of the duration of the maternal infection.

Information regarding the duration of syphilis in the patients in our study was based chiefly on serologic tests and dark-field examinations made in this hospital or in the venereal-disease clinics. Most of the patients had attended the hospital clinics for many years, and a number of routine serologic tests had been taken prior to their pregnancies. The results of these tests and the clinical history of syphilis as obtained from the patient enabled us to determine with reasonable accuracy the duration of syphilis in 57 of the 77 patients. It was noted that 53 of the 57 patients in whom the duration of the disease could be determined had acquired syphilis or an infectious recurrence less than five years before delivery of the syphilitic child. This information was based on a definite record of negative serologic tests within five years previously or on a positive dark-field examination during that period. Fourteen of the 53 patients had acquired an initial syphilitic infection as long as eight years or more before delivery of the syphilitic child. These 14 patients, however, received sufficient treatment to produce a negative serologic test within four years prior to delivery, and then had either a relapse of the initial infection or a reinfection that was transmitted to the infant.

Only 4 patients were known to have a persistent infection for more than five years prior to the birth of a syphilitic child. This information is based on a record of a positive serologic test five or more years before delivery. Two of these 4 patients had had syphilis more than six and seven years before delivery and were among those discussed above as having had negative and doubtful serologic re-

actions in this pregnancy resulting from insensitivity of the tests. The remaining 2 women with late syphilis had acquired the infection about seven and eleven years previously and had never received treatment prior to delivery of the infected child. The fact that patients such as these, with late syphilis, can deliver infected children, appears to support the current practice of treating syphilis in pregnancy regardless of the duration of the disease.

TREATMENT BEFORE PREGNANCY AND OUTCOME OF PREGNANCY

The pregnant syphilitic woman has always been regarded as a potential source of infection for the fetus, even though she may have had sufficient treatment to prevent the transmission of the disease to her marital partner. For this reason, re-treatment of syphilis in pregnancy has been advised regardless of the amount of therapy the patient may have received previously. Recently, this concept has been questioned, and antisyphilitic therapy in pregnancy has been deliberately omitted in a series of selected patients who had had what was considered adequate arsenical or penicillin therapy prior to pregnancy. Goodwin and Farber⁷ have reported the outcome of pregnancy in 385 patients, 22 of whom had been treated with penicillin alone. These patients have been observed through 570 pregnancies, none of which resulted in a syphilitic infant. The adequacy of penicillin in protecting the fetus from syphilitic infection in subsequent pregnancies has also been studied by Ingraham and his associates,⁸ who found that none of 52 women treated for syphilis before, but not during, pregnancy delivered syphilitic children. These workers emphasized that the patients in whom treatment in pregnancy is to be omitted should be carefully selected and that constant observation should be made during pregnancy for evidence of serologic or infectious relapse.

Approximately three fourths of the 77 women in our study had not received any treatment for syphilis before the pregnancy that resulted in a syphilitic child. Only 5 patients were thought to have had "adequate" treatment before pregnancy,⁴ of these had been given from 16 to 32 injections of an arsenical and bismuth preparation each, and 1 patient had been treated with more than 2,000,000 units of penicillin. In all 5 women, however, the syphilitic infection recurred (manifested by either infectious lesions or serologic relapse) just prior to or during the pregnancy that resulted in a syphilitic infant. None of the women had received any treatment for the recurrent infection before pregnancy.

It appears, therefore, that the interpretation of what constitutes "adequate" therapy before pregnancy depends not so much upon the amount of treatment administered as upon the course of the disease after therapy. Treatment of syphilis

THROMBASTHENIA AND THROMBOCYTOPENIC PURPURA*

Report of Case Demonstrating Qualitative and Quantitative Inadequacy of Platelets

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RECENT advances in the knowledge of blood coagulation clarify understanding of the hemostatic defect underlying various hemorrhagic disorders. The pathogenesis of hemorrhagic disease is usually attributable to disturbed retractility of the small blood vessels, as in vascular and allergic purpura, thrombocytopenia, deficiency of anti-hemophilic "globulin" — hemophilia[§], insufficiency of prothrombin or its accessory factors — for example, hypoprothrombinemia, parahemophilia,² deficiency of prothrombin A³ and accelerator globulin deficiency⁴, fibrinopenia, and presence of circulating anticoagulants — heparin⁵ or heparin-like substances.⁶

There are, however, clinical conditions in which the nature of the hemostatic dysfunction is obscure, such as those designated as "hereditary hemorrhagic thrombasthenia"⁷ and "pseudohemophilia"^{8,9}. Glanzmann⁷ ascribed hemostatic failure in his subjects to a qualitative abnormality of the platelets because of their bizarre appearance and delayed clot retraction. Von Willebrand and Jürgens⁸ also described platelet abnormalities in their patients, and concluded that the hemorrhagic phenomena were due to defective platelet agglutinability.

The purpose of the present communication is to report data in a patient with pseudohemophilia that demonstrate that the hemorrhagic tendency was associated with a qualitative defect in the patient's platelets despite their normal number. Subsequently, the patient developed thrombocytopenia suggesting a possible relation between purpura of the Glanzmann and von Willebrand type and idiopathic thrombocytopenic purpura.

CASE REPORT

A 40-year-old married truck driver (P B B H 384)¶ was admitted to the Peter Bent Brigham Hospital on March 27, 1949, because of hemorrhage. One month before, he had noted bleeding from the palate, gums and nose, and expectoration of blood-streaked sputum. Six days prior to admission he experienced corvza and slight cough, and observed small red spots on his leg. He took several "four-way cold tablets" (aspirin, quinine, magnesium hydroxide and phenol-

phthalein). He was also aware of easy bruising and some hematuria. Except for a bilateral epistaxis 2½ years before admission there had been no hemorrhagic phenomena.

The family history revealed no bleeding tendency in the parents, or in 3 sisters and 1 brother.

At age of 18 the patient had gonorrhea, and he remembered an indurated, painless "cold" sore on his lip that could have been a chancre. After the incidental discovery of a positive serologic test in 1943 he received 4 courses of Mapharsen and 5 courses of bismuth. In 1945, because of a persistently abnormal spinal fluid, he was given 10 paroxysms of malarial fever and 13 2-gm doses of Triparsamide. There had been no neurologic, cardiac or genitourinary symptoms.

For several years the patient had been taking 1 teaspoonful of "Bismarex" or "Bisodol" daily because of epigastric postprandial distress. (These antacids contain bismuth subcarbonate.) The past history was otherwise irrelevant. There had been no exposure to other drugs or toxic chemicals, and there was no allergic history.

Physical examination revealed a well developed, well nourished man with confluent purpura over the arms, hips and thighs. The pupils were Argyll-Robertson in type. The mouth showed petechial hemorrhages on the hard palate, upper gums and buccal mucosa. The lower gums, which revealed some gingivitis, bled on pressure. There were a few small cervical submandibular and left axillary lymph nodes. The lungs and heart were normal. The liver and spleen were not palpable. Reflexes were normal. The blood pressure was 135/70. X-ray study of the abdomen and bones was negative.

The urine was normal except during the first several days, when the sediment was packed with red cells. Examination of the blood revealed a red-cell count of 4,200,000, with a hemoglobin of 14.1 gm per 100 cc, a hematocrit of 43 per cent and a normal white-cell count. For the first several days the smears showed abundant platelets.

On March 28 the platelet count was 204,000, the bleeding time (Duke method) 65 minutes and the clotting time 6 minutes (Lee-White method). The clot failed to retract within 32 hours. The prothrombin time was 17 seconds (control, 17 seconds). Capillary fragility (Rumpel-Leede technic) was markedly positive. On April 3 the bleeding time was 25 minutes, and the clotting time 9 minutes, clot retraction again was poor. On April 9 capillary fragility was again markedly increased. On April 13 the platelet count was 8000. On April 23 the bleeding time was 5 minutes, and the clotting time 8 minutes, the clot failed to retract. No platelets could be seen on the blood smear. On April 5 the platelet count was 25,000. A bone-marrow aspirate showed numerous megakaryocytes by direct smear and in fixed section. Two protamine-heparin titration tests were normal.

The stools consistently showed + to ++++ tests for occult blood.

Because he showed progressive clinical improvement despite the thrombocytopenia that developed, the patient was discharged on April 5 to return to the Out-Door Department for further observation. The low platelet count, high bleeding time and increased capillary fragility have persisted till the present time.

Studies of the Coagulation Defect||

Methods. Platelets were counted by the Rees-Ecker method.¹⁰ Recalcification times were determined at room temperature on oxalated plasma (1 part of one-tenth molar sodium oxalate to 9 parts of blood) to which was added one-fifth volume of 1 per cent calcium chloride solution.

Plasma prothrombic activity was determined by the modified one-stage procedure of Rosenfield and Tuft,¹¹ in which

||The data recorded in this section were obtained in the Medical Research Laboratory of the Beth Israel Hospital.

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¶It is still uncertain whether hemophilia is referable to a deficiency in anti-hemophilic globulin or to a circulating anticoagulant anti-cephalin or both.

¶We are indebted to Drs. Clement Finch and Stuart Finch of the Peter Bent Brigham Hospital, Boston, for making this case available for study. The data in the case report are from the records of that hospital.

or became delinquent after a few treatments. Although the use of penicillin in such patients would have prevented some of the congenital infections, there is no doubt that the prevention of congenital syphilis is largely a matter of public-health education. Women should be urged to seek prenatal care early in pregnancy.

In a few cases the attending physician did not establish the diagnosis of syphilis sufficiently early or did not institute immediate or vigorous anti-syphilitic therapy. Several of our patients were attended by private physicians, who neglected to take blood for serologic tests.

SUMMARY

A clinical study of the factors responsible for the transmission of infantile congenital syphilis was made by a review of the records of 77 women who delivered syphilitic infants.

Approximately a fourth of these women had negative serologic tests for syphilis in pregnancy and, for this reason, had not received any prenatal treatment for syphilis. The majority of these patients are believed to have been in the incubation period of the disease at the time of the negative test, or to have acquired an initial or recurrent syphilitic infection later in pregnancy. The importance of repeating serologic tests near term to detect syphilis acquired late in pregnancy is emphasized.

The duration of the maternal infection was almost always less than five years prior to birth of the syphilitic infant. An occasional patient transmitted syphilis to her child even though she had

had the disease for as long as eleven years previously.

Half the women who were given prenatal treatment had received 11 to 20 injections of arsenoxide during pregnancy. The inadequacy of arsenical therapy given late in pregnancy is pointed out. Penicillin therapy is believed to be the treatment of choice in prenatal syphilis and will probably result in a considerable reduction in the incidence of congenital infection.

The most important measure, however, in the prevention of congenital syphilis is greater education of pregnant women, who should be urged to seek prenatal care early in pregnancy.

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the family does not exclude this interpretation since in many cases a positive family history cannot be elicited.⁹

The experimental data, obtained during this time, also were like those found in thrombocytopenic purpura — namely, high residual serum prothrombic activity and prolonged recalcification time. Since normal platelets added to the patient's deplateletized plasma rectified this clotting defect, and conversely, addition of the patient's platelets to normal plasma deprived of its platelets did not correct the abnormality thus induced, one must conclude that the patient's platelets were inherently defective and unable to function normally. The addition of normal platelets to thrombocytopenic blood similarly corrects its clotting defect.¹³ Thus, except for the normal number of platelets, the patient's blood was indistinguishable from thrombocytopenic blood.

Progression of the disease to thrombocytopenia is of considerable interest. Had the patient been first seen at this point, a diagnosis of idiopathic thrombocytopenic purpura would have been considered correct. It is difficult to relate the underlying condition to the syphilis or to possible acquired sensitivity to bismuth, which the patient had been taking in the form of antacids. The finding of a normal bone marrow containing numerous megakaryocytes helps exclude thrombocytopenia on the basis of chemical destruction.

The sequence of thrombocytopenia following thrombasthenia suggests the possibility that idiopathic thrombocytopenic purpura is sometimes preceded, if only for a short time, by abnormal platelets that are removed from the circulation. In this connection, previous observations¹³ on a patient with thrombocytopenic purpura treated by splenectomy may be significant. Although the platelet count in this subject returned to normal after the procedure, coagulation was still abnormal, suggesting some qualitative inadequacy of the platelets. She suffered a relapse within a few months.

Means are now available to detect functional abnormality of platelets in patients with hemorrhagic phenomena. The finding of abnormally high residual prothrombin in the serum indicates inadequate conversion of prothrombin to thrombin. A normal plasma prothrombin time will exclude as its cause deficiency of any factor in the prothrombin constellation — labile factor, prothrombin A, accelerator-globulin, factor V or the factor of Fantl and Nance¹⁷ as well as fibrinogen. Subnormal prothrombin conversion can then be referable only to inadequate evolution of thromboplastin that is due to hemophilia, which can be readily excluded, thrombocytopenia, thrombasthenia or circulating anticoagulants. The last is easily demonstrable by the prolonged clotting time as well as the retarding effect of the plasma in question on the clotting time of normal blood or plasma.

No method for precise measurement of the functional capacity of platelets has yet been devised. On the basis of the above observations one might propose the following procedure: addition of the platelets in question to normal plasma, drawn and deprived of its platelets with meticulous precautions against platelet breakdown according to the technic of Brinkhous.¹⁴ The mixture of normal platelet-free plasma with the platelets to be studied could then be recalcified, and residual serum prothrombic activity determined. Normally no prothrombin should be demonstrable. The amount of prothrombin remaining in the serum should be a measure of thromboplastin evolving from the platelets since all other clotting factors important in prothrombin conversion will have been provided or adequately controlled. This method is being evaluated.

SUMMARY

Functional inadequacy of platelets (thrombasthenia) associated with hemorrhagic phenomena occurs. This was demonstrated by observations on a patient with purpura, elevated bleeding time, increased capillary fragility, poor clot retraction, normal platelet count and normal clotting time. He showed a coagulation defect indistinguishable from that observed in thrombocytopenic purpura, reflected in an elevated recalcification time and high residual serum prothrombic activity.

This could be rectified by the addition of normal platelets to the patient's deplateletized plasma, whereas the patient's platelets were unable to correct the coagulation defect induced in normal plasma by deprivation of its platelets.

The platelet count, at first normal, later dropped to thrombocytopenic levels. This suggests a possible relation between thrombasthenia and idiopathic thrombocytopenic purpura.

The detection of thrombasthenia is discussed. A method for measuring the functional capacity of platelets is proposed.

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normal plasma rendered prothrombin-free by adsorption with barium sulfate is used as a diluent for the test plasma. Residual serum prothrombic activity was similarly measured on serum from blood allowed to clot spontaneously, or from oxalated plasma that was recalcified.¹² The serum was separated 1 hour after coagulation, oxalated (1 part oxalate to 4 parts serum), and then incubated for 15 to 30 minutes at 37°C to inactivate thrombin.

Results On March 29 the patient had 275,000 platelets per cubic millimeter of oxalated plasma (well within the normal range in our laboratory). Plasma prothrombic activity was 90 per cent, whereas the residual serum prothrombic activity (one-stage method) was 130 per cent. This observation, in agreement with those obtained in thrombocytopenia,¹³ indicated a distinct coagulation defect despite the normal platelet count and clotting time.

Further studies were done in which the patient's platelets were transferred to deplateletized normal plasma and normal platelets transferred to deplateletized patient plasma. On March 31 oxalated plasma (158,000 platelets per cubic millimeter) from the patient and from a normal subject (182,000 platelets per cubic millimeter) were centrifuged at 15,000 r p m in the multispeed attachment of the International Centrifuge for 15 minutes at 7°C. The supernatant

The following additional observations were made on April 4 the patient's platelet count was 212,000 per cubic millimeter of whole blood, and plasma prothrombic activity was 106 per cent, whereas residual serum prothrombic activity was 95 per cent. On April 7 the plasma contained 84,000 platelets per cubic millimeter. The patient's residual serum prothrombic activity was still elevated (80 per cent of the parent plasma). On April 11 the platelet count was 57,000 per cubic millimeter of capillary blood and 50,000 per cubic millimeter of oxalated venous blood.

The accelerating effect of the patient's plasma on the coagulation of blood from a patient with known hemophilia was normal. This helped exclude a diagnosis of hemophilia.

It is thus evident that early in the course of the disease, despite the normal platelet count, the patient's blood showed the following evidence of defective coagulation: prolonged recalcification time and high serum prothrombic activity. This could be rectified completely by the addition of normal platelets to the patient's deplateletized plasma, whereas the patient's platelets could not correct the abnormality induced in normal plasma by removal of its platelets.

Within 2 weeks of admission thrombocytopenia developed and has persisted until the present.

DISCUSSION

Although the role of platelets in the hemostatic mechanism is not entirely understood, certain facts have been clearly established. Reduction in platelet number is associated with hemorrhagic phenomena, prolonged bleeding time, abnormal clot retraction and disturbed capillary retractility. Also, a clotting defect has recently been demonstrated in spontaneous thrombocytopenia and in blood from which the platelets are artificially removed: coagulation is retarded,¹⁴ prothrombin consumption is reduced, and residual prothrombic activity in the serum is elevated.^{13, 15} This is in accordance with the general opinion that the platelets are required for the elaboration of thromboplastin.

The degree of thrombocytopenia necessary to induce the clinical and laboratory manifestations of purpura varies from patient to patient,¹⁶ and suggests that qualitative differences in the platelets are important. Furthermore, the existence of normal platelet counts in cases demonstrating many features commonly associated with thrombocytopenic purpura raises suspicion that the quality of the platelets in these subjects may be poor.

The observations in the case reported above indicate that such aberrations in platelet function actually occur. Early in the course of his disease the patient showed the salient clinical manifestations of thrombocytopenic purpura despite normal platelet counts: bleeding into the skin and from the mucous membranes, increased bleeding time, normal clotting time, increased capillary fragility and poor clot retraction. Although this case may have been unique, these features justify a diagnosis of "thrombasthenia" or "pseudohemophilia," since in this syndrome the platelet count is usually normal, the bleeding time is variable, the clotting time of venous blood may be normal or increased, clot retraction is usually normal but may be poor, and capillary fragility may be normal or markedly increased. The absence of a bleeding tendency in

TABLE 1 *Abnormal Platelet Function in a Patient with Thrombasthenic Purpura*

TYPE OF PLASMA	PLATELETS <i>per cubic millimeter</i>	PROTHROMBIC ACTIVITY		RECALCIFICATION TIME <i>min</i>
		PLASMA	SERUM	
		%	%	
Patient				
Whole	158 000	90	150	11
Deplateletized	14 000	—	42	30*
Deplateletized plus Normal platelets	235 000	—	0	5
Normal subject				
Whole	182 000	90	0	6
Deplateletized	18,000	—	30	30*
Deplateletized plus Patient's platelets	167 000	—	15	11

*Approximate values

plasmas, carefully separated from the platelet pellets, contained 14,000 and 18,000 "platelets" per cubic millimeter respectively.

The sediments were washed twice with physiologic saline solution. The patient's platelets were then dispersed with vigorous agitation in a volume of platelet-poor normal plasma equivalent to the plasma from which the patient's platelets were derived, giving a mixture with a final platelet count of 167,000 per cubic millimeter. Similarly, the normal platelets were suspended in the patient's plasma, yielding a final count of 235,000 per cubic millimeter. Recalcification times and residual serum prothrombic activities were determined.

The recalcification time of the patient's whole plasma was distinctly greater than normal (Table 1). As anticipated, removal of platelets from both types of plasma retarded coagulation considerably. Addition of normal platelets to the patient's deplateletized plasma restored the recalcification time to normal. In contrast, the recalcification time of the normal plasma containing the patient's platelets was abnormally prolonged, and was the same as that of the patient's whole plasma.

The prothrombic activity of serum obtained from recalcification of the patient's whole plasma exceeded that of the parent plasma, as did serum from the patient's blood allowed to clot spontaneously (as described above). In contrast, serum similarly derived from whole normal plasma showed no prothrombic activity. Recalcification of normal plasma deprived of its platelets yielded serum that contained substantial prothrombic activity. This was somewhat reduced when the patient's platelets were added to the platelet-poor normal plasma. However, serum obtained from a mixture of normal platelets with the patient's platelet-poor plasma was devoid of prothrombic activity just as serum obtained from whole normal plasma.

not between right and wrong, but between good and better, and so discrimination and good taste are continually sharpened and polished by practice. Most serious educators will still agree with the thesis that the main purpose of education is to teach one how to think rather than what to think. Yet modern education seems more and more exclusively to offer opportunities for the simple accumulation of usable facts. Such factual knowledge, without the wisdom to apply it, is of limited value. Osler once made the following penetrating statement:

After all, the greatest difficulty in life is to make knowledge effective, to convert it into practical wisdom. We often confuse the two, and we think they are identical. But, far from being one, they often have no connection whatever.

Wisdom is the result of experience in a man who can profit by it because he has cultivated the ability to use his mind well. Unfortunately for the future, the medical student is a tender plant more often watered with a jet of "scientific method" than with the gentle rain of culture, so knowledge grows while judgment withers.

It is a reflection on the critical faculty of physicians that a spark, kindled in 1928 by Fleming, was allowed to smoulder unheeded for over ten years before it burst into therapeutic flame, and that Mendel's doctrine was allowed to hibernate for thirty years before it saw the light of recognition. Again, the Schemm regime is often thought of as an innovation. It is overlooked that, as Dr Schemm himself recalls, Sir Thomas Witherly reported in 1690 his winecooper who cured his own prodigious dropsy by ingesting 14 quarts of water in ten hours.

Such flowers of progress are left to blush unseen in the dark, unfathomed recesses of the library stacks, while doctors busy themselves about their little, self-important papers, intent on adding their special "gem" to an already embarrassing wealth of publications. They are apt to forget that the empty vessel makes the greatest sound. Such a premium is set on "getting something published" that the journals are too often full of forests of trivialities in which one cannot see true landmarks for the trees.

Finally, a classical education can be of help by giving an interest in a really beautiful study: the study of peoples in their prime, of civilizations at their best, of poetry and drama in their heyday. This may seem flat and unprofitable to the exclusive moneymaker, but it is an interest that time does not destroy. Education is the only worldly possession that cannot be lost until one loses one's senses. Moreover, the average patient prefers to consult a doctor with an education and a soul — and so it has even its material reward.

When the soured, thrombosed moneymaker retires to live on his store of gold, how empty is his existence compared with that of his colleague who has developed "occupations that will render life more dignified and useful." He must either fall into the spinsterly prerogative of minding other people's businesses or else resign himself to stale and weary boredom. As Osler said so well, "You may find too late, with hearts given away, that there is no place in your habit-stricken souls for those gentler influences which make life worth living."

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ACRIBIA

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BALTIMORE

THE practice of medicine is said to be an art as well as a science. Certainly at its best it is a happy blend of both. But today science is nurtured at art's expense, with the unhappy result that doctors are more and more enthralled by numbers and devices, and less and less concerned to cherish precision of their own. Yet this personal precision is as much to be desired as it is sorely lacking, both in clinical skill and in literary expression. The Greeks, as usual, had a word for it, *ἀκρίβεια*, whose shades of meaning have been well translated "exactness, literal accuracy, precision, niceness of sense." Hippocrates, who called medicine "The Art" (and there was little that one would call "scientific" in his art), emphasized the need for this faculty. This need is as great today as it was yesterday.

With so much in medicine that is still inexact, it is the greater pity that inaccuracies have been allowed to taint the medical vocabulary. When a disease is named, for instance, one should be sure one knows what the adopted word means. Yet "erythromelalgia" has recently been attached uncomfortably to a form of headache. This is as good, or as bad, an example as one can hope to find of the crime that Oliver Wendell Holmes called "verbiage." In this particular case there is less than usual excuse, because Weir Mitchell, in his original description of the disease, adds an explicit footnote to his title, "the foot and hand disorder I am about to describe may be conveniently labeled Erythro-mel-algia, ἐρυθρός, red, μέλος, a member, ἄλγος, pain." Thus the new syndrome, "erythromelalgia of the head," can only mean, if words mean anything, "pain in the red limbs of the head," which is anomalous to say the least. If an affection of the head, analogous to erythromelalgia, is to be given a name, "erythrocephalgia" is all that is required. Another lapse is the not infrequent use of "anhidrosis" for "absence of sweating." This is a natural enough mistake, supposedly because the writer believes that the word is compounded from the stem hydro- (water), it is of course derived from ἰδρῶς (hidros), sweat,

and the word is, and has been for 2400 years since Hippocrates used it, anidrosis, or often with the "h" retained, anhidrosis. "Pruritis" is another misbegotten child, the word is pruritus, and has nothing to do with the "-itis" that usually connotes inflammation. Its ending is the same as that in tinnitus and exitus, and it has survived and been used by medical writers since the time of Pliny (70 A.D.). Therefore, it deserves at least the respect of age.

Such inaccuracies may seem trivial, and, indeed, in themselves, they are. But they are a symptom of a too prevalent syndrome, the etiology of which is indifference for literal accuracy, and indeed for any education that aims at "niceness of sense" without being strictly utilitarian. If the matter is given any careful thought, however, there are many apparent reasons why a cultural, nonscientific education, including a more than passing knowledge of the classical languages, is of great and lasting value to physicians. It is an asset that will accumulate interest with the passage of the years. For "the real object of education is to give children resources that will endure as long as life endures, habits that time will ameliorate, not destroy, occupations that will render sickness tolerable, solitude pleasant, age venerable, life more dignified and useful, and death less terrible."

First, and least important, a classical education makes the understanding of medical terms easier and more interesting, and therefore encourages a more exact and careful usage of them.

Secondly, it teaches the English language better than any other form of education. The mental gymnastics that are inevitable (because of the entirely different classical idiom) in construing from Latin and Greek into English, and vice versa, teach one the meaning and use of one's own tongue as nothing else can. The writings of medical men are consistently referred to as "literature," but that dignity is seldom deserved.

Thirdly, the classics are a real education in the sense that they teach one *how* to think. No other training so constantly involves the exercise of judgment. There is always a decision to be made,

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physiologic role of vitamins, as well as leading to the discovery of new substances, but the limitations of this review permit no more than occasional reference to them. Answers to the questions posed will be approached through the following major subdivisions: standards of minimal and optimal vitamin intake, nutritional surveys and subclinical vitamin deficiency, reports of specific therapeutic uses of vitamins, newer vitamins, toxicity of vitamins, and antivitamins and vitamin imbalance.

STANDARDS OF MINIMAL AND OPTIMAL VITAMIN INTAKE

A knowledge of the minimal requirements for the various vitamins is an aid in evaluating the need for wholesale supplementation of the American diet with multivitamin capsules. Commercial advertising frequently stresses a widespread inadequacy of vitamins in food intake. The validity of these claims is open to question when the available information about minimal requirements and limitations of vitamin therapy is reviewed. Opinion varies about what constitutes the minimal requirement for any given vitamin. One theory is that the minimal requirement is the smallest amount sufficient to prevent clinical manifestations of deficiency. This value can be determined for thiamine, vitamin C and with less certainty for vitamin A, riboflavin, niacin and vitamins D and K—that is, vitamins in whose absence or deficiency specific signs or symptoms of avitaminosis have been recognized in man. In view of the fact that most deficiencies are multiple,³⁻⁶ the clinical determination of minimal requirements has depended upon the experimental production of a specific deficiency by restriction of that vitamin. An objection to this approach is that such conditions are abnormal and, with thiamine at least, reduction of intake may affect body metabolism and secondarily its thiamine requirement.¹¹ I believe that such an objection is more theoretical than actual and that determination of minimal vitamin requirement by the experimental production of a clinical deficiency is a valuable technique.

The clinical investigation of requirements for the other known vitamins is limited by the absence of specific signs or symptoms of deficiency in man. Large body stores of some vitamins and endogenous synthesis of others add to the difficulties of establishing the minimal demands.

There are many investigators who believe that the minimal requirement for a vitamin should prevent subclinical deficiency,³⁻¹² a state of physiologic and biochemical derangements that cannot be detected clinically.¹¹ The need for more delicate methods for defining subclinical deficiency has led to biochemical and biologic measurements of blood and urinary excretion levels for some of the vitamins. There is great variation in the analytical methods

and little agreement concerning what level of tissue saturation represents the critical point of subclinical deficiency for any given vitamin. I wonder if the biochemical level below which a subclinical deficiency exists varies with the emotional bias of the investigator toward clinical or subclinical deficiency standards and with his enthusiasm for vitamin therapy. Moreover, the blood levels of vitamin A¹³ and the urinary excretion values of riboflavin, N-methyl nicotinamide, biotin and folic acid may remain relatively constant for long periods in spite of changes in intake or may fluctuate greatly without correlation with intake or with physical status of the patient.¹⁴⁻²⁰ For these reasons it is difficult to establish by laboratory methods which levels indicate the minimal requirement of various vitamins necessary to prevent a subclinical deficiency.

Vitamin A

Man has such large stores of vitamin A in his liver²¹ that determinations of the minimal requirement by experimental development and prevention of clinical signs of vitamin A deficiency have been difficult and few. On the basis of animal studies, Embree⁷ has estimated that the minimal requirement of vitamin A is one tenth of the optimal requirement. If this estimation can be applied to man, the minimal requirement might be 500 to 600 international units per day. By maintaining a normal subject on a vitamin A deficient diet for approximately 598 days, producing a significant fall in the plasma vitamin A level from 133 to 76 IU, Hartzler²² found that administration of 2000 to 3500 IU of vitamin A per day was sufficient to stabilize the plasma level or even raise it slightly.

Using the maintenance of normal dark adaptation as the end point, another investigation²³ showed that the minimal requirement for vitamin A averaged 40 IU per kilogram of body weight in 5 subjects (range, 25 to 56 IU). For a man weighing 70 kg this would require 2800 IU of vitamin A. However, many investigators think that the dark-adaptation method is unreliable. These limited studies suggest that any intake above 3000 IU of vitamin A per day is adequate, but, in calculating the intake, one must make allowance for the large proportion of unavailable carotene in vegetables.²³

Thiamine

Studies of minimal requirements have been more extensive for thiamine than for other vitamins, possibly because the symptoms of thiamine deficiency dominate the picture of vitamin B inadequacy.¹⁴ If the minimal requirement is based upon prevention of clinical symptoms, two reports²⁴⁻²⁵ from China and the Philippines agree that 0.4 mg of thiamine per 1000 calories is the critical level of intake, below which frank beriberi appeared. The re-

MEDICAL PROGRESS

VITAMIN SUPPLEMENTATION IN HEALTH AND DISEASE*

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BOSTON

THE importance of vitamins in nutrition has been so forcefully and repeatedly stressed by radio, newspaper and word-of-mouth advertising that the general public is most receptive to the inclusion of vitamin supplements in daily diets. Any report that implies or promises alleviation of chronic or incurable illness by the use of a vitamin preparation excites further demand for vitamins. The magnitude of vitamin consumption in this country is evidenced by the fact that the annual sale of vitamins in the United States amounted to \$188,000,000 in 1947¹. There was a 300 per cent increase (from \$15,000,000 to \$45,000,000) in the sale of costly, high-potency preparations between 1945 and 1947. The commercial outlets for vitamins¹ showed that a considerable proportion of the sales are for self-prescribed vitamins rather than for those on physician's prescription. Of the total \$188,000,000 sales in 1947, \$26,000,000 were made through mail-order houses, department stores, grocery stores and variety stores.

That the public is not alone in its intense interest in vitamins is manifest. In the last four years since the subject of vitamins was reviewed,² three or four thousand articles covering various aspects of vitamins have appeared in medical journals throughout the world. Among these were several careful surveys of specific topics.

Cowgill³ presents a conservative but thought-provoking discussion of some of the clinical applications of research in the field of vitamins. Salient points include a consideration of the causes for great individual variation in vitamin requirements, the controversial topic of subclinical vitamin deficiency, the nonspecificity of the so-called signs of vitamin deficiency, and mention of some vitamin interrelations and of antivitamins. Cowgill's paper does not pretend to be encyclopedic, it is, rather, a delightful discussion of some recent advances in the knowledge of vitamins.

A concise, factual tabulation of all the vitamins, with brief outlines of their chemistry, indications and requirements, is presented by Harris.⁴ Useful information about the members of the vitamin B complex is completely reviewed by Elvehjem.⁵ This paper deserves attention. Gnipwall⁶ emphasizes

subclinical states of vitamin B deficiency and discusses etiologic factors but data to support some of his statements are lacking. In addition, he is inconsistent. He indicates the need for massive doses (20 to 40 mg) of thiamine and then discusses a case of ariboflavinosis that developed after therapy with thiamine. He appears to recognize vitamin imbalance but does not consider it in his therapeutic advice.

The role of the fat-soluble vitamins is discussed in a brief but fairly complete review by Embree.⁷ The history of folic acid up to 1947 and its therapeutic uses are covered by Sargent.⁸ One final review is an excellent summary of antivitamins. Wright⁹ discusses this complex subject in simple, understandable terms.

In view of the large number of conflicting reports concerning the beneficial effect of various vitamin supplements, another review of the vitamin literature published during the last four years, with emphasis upon vitamin requirements and on the value of vitamin supplements, seems timely. The following questions are considered.

Is there objective evidence to justify such a tremendous use of vitamin supplements?

Does the promiscuous ingestion of vitamins benefit public health or promote recovery from disease?

Can overindulgence in vitamins cause harm beyond deflation of the public pocketbook?

It is difficult to answer these questions without emotional bias. There are increasing manifestations that the vitamin fad is passing and that a more conservative view of their therapeutic value is developing. Several recent reports stress a well balanced diet as preferable to purified vitamin supplements.^{3, 5, 6, 10} It is my opinion, however, that as long as the public believes in the magic of vitamins, the physician will be forced to prescribe them, although he may not anticipate any benefit beyond a psychologic one. Moreover, practitioners are carefully informed of all progress in the therapeutic use of vitamins by manufacturers who, for obvious reasons, favor reports that stimulate sales.

In this review, the continued reports on small numbers of well recognized specific deficiency states are not discussed. The results of animal and bacteriologic experimentation are slowly revealing the

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in the urine in twice the quantity excreted when it was taken in equal amounts between meals³⁵

Further investigations indicated that thiamine requirements may be increased for the first week after severe burns or injury, as shown by low urinary excretion in spite of daily intakes of 3 mg of thiamine^{36, 37}. Confirmation of these observations will require further investigation with larger supplements of thiamine to prove that the post-traumatic decrease in urinary excretion is due to increased thiamine utilization and not to other factors. I have not discovered any other controlled studies within the last four years that demonstrate an increased demand for thiamine during various disease states. The apparent effect of an elevated metabolic rate upon increasing thiamine utilization has been summarized previously.³⁵

On consideration of all these reports on various investigations into the minimal requirement for thiamine and into the factors that may modify it, it seems justifiable to conclude that an intake of 0.26 to 0.35 mg per 1000 calories with consumption of at least 0.7 mg per day, is a reasonable approximation of the minimal requirement for thiamine.

Riboflavin

The amount of riboflavin required by man to prevent clinical or subclinical deficiency has not been determined with any certainty. During the last four years there have been no reports of success in the experimental production of clinical riboflavin deficiency. Volunteers have lived on 0.3 mg per 1000 calories for one hundred and sixty-one days⁴⁴ and on 0.28 mg per 1000 calories for more than a hundred days⁴⁹ without any evidence of ariboflavinosis. Either a much greater restriction of riboflavin intake or the introduction of other unknown factors is required for the development of the clinical findings characteristic of riboflavin deficiency.

It is impossible to define subclinical deficiency on the basis of the urinary excretion of riboflavin because many factors in addition to the quantity of riboflavin consumed affect urinary excretion. Oldham et al.⁴⁰ found that there was a striking inverse relation between urinary riboflavin excretions and nitrogen balances. Under conditions of a constant intake of riboflavin, the urinary excretion varied from 40 to 60 per cent of the intake during periods of strong negative nitrogen balance to only 7 per cent when the subjects were in positive nitrogen balance. These observations confirm and extend the work of Andreae et al.,⁴¹ who showed that there was a retention of 0.3 mg of riboflavin with each gram of nitrogen retained. Moreover, this nitrogen-riboflavin relation explains the marked fluctuations in riboflavin excretion subsequent to burns and injury^{36, 37, 41} and opens to question any

statements about the increased requirement for riboflavin after trauma.

There is ample evidence of intestinal synthesis of riboflavin, which can be greatly modified by the type of diet ingested.⁴² During periods of low riboflavin intake, fecal excretion of riboflavin may exceed the amount provided in the diet.³⁹ The demonstration of considerable amounts of "free" riboflavin in the feces suggests the possibility of utilization of riboflavin synthesized in the intestine when oral intake is low.⁴² To date no one has proved that the riboflavin from intestinal synthesis is absorbed. In view of these nondietary factors which may alter the level of urinary excretion of riboflavin it is surprising to note the agreement of different investigators concerning the correlation of urinary excretion with the quantity ingested when the dietary intake of riboflavin is 1.4 mg or less.⁴² Regardless of the factors that complicate interpretation, there have been attempts to estimate the riboflavin requirement proceeding on the assumption that urinary excretion reflects tissue saturation. Davis et al.³⁹ found that there was urinary excretion of 40 per cent of the increment in riboflavin intake between 1.02 and 1.23 mg. At higher levels of intake approximately the same percentage of the increment was excreted whereas at intake levels below 1 mg very little of the increment was excreted. These findings are interpreted as indicating that there is tissue saturation with riboflavin at an intake of 1.23 mg per day and that this quantity of the vitamin meets the human requirement. Brewer et al.⁴³ observed a similar change in urinary excretion of riboflavin when the intake exceeded 1.3 to 1.5 mg per day. They define this level as the "optimal" intake of riboflavin or upper limit at which there is economical utilization of the substance.

A final comment about the requirement for riboflavin is the change from computing it on the basis of caloric intake to computing it on the basis of 0.020 mg per body weight.⁴⁴ To summarize the observations on riboflavin requirements, I believe that 1.0 mg per day is more than adequate to prevent subclinical ariboflavinosis.

Niacin

There are very few data about niacin requirements in man. Niacin (nicotinic acid) and nicotinamide are equally effective therapeutically.⁴⁵ In practice nicotinamide is preferred because its administration is not associated with the unpleasant side effects caused by niacin. In this discussion, the word niacin refers generically to both substances.

The experimental production of clinical niacin deficiency in man has not been reported. No signs or symptoms of niacin lack were observed in a group that consumed 5.8 mg per day for fifteen to eighteen weeks.⁴⁶ Tissue stores of niacin may be sufficient to meet ordinary demands for long periods and in-

quirement in both these reports was probably somewhat higher than that under normal conditions because of poor, unbalanced diets, diarrhea and the increased demands of pregnancy.

On the basis of experimental development of symptoms of thiamine deficiency by restricting the intake at varying levels, Foltz et al²⁶ concluded that the minimal daily requirement for young men ranged from 0.33 to 0.45 mg per 1000 calories. In a carefully controlled study lasting one hundred and sixty-one days, Keys et al¹⁴ observed that a thiamine intake of 0.185 mg per 1000 calories, together with restriction of other B vitamins and a 3300-calorie diet, was without significant effect on "fitness," health and personality. After four weeks at this level of intake, there was a 0 urinary excretion of thiamine. That the body reserves of thiamine were being depleted during this period of restriction was evidenced by the rapid deterioration of these subjects when there was further restriction of the thiamine intake to 0.008 mg per 1000 calories. The rapidity of this deterioration was striking in comparison with that in a control group that had been receiving a supplement of 1 mg of thiamine per day before the acute restriction to 0.008 mg per 1000 calories. On the basis of their studies, Keys et al¹⁴ are of the opinion that 0.23 mg of thiamine per 1000 calories is adequate.

In another well controlled investigation with restriction of thiamine to 0.5 mg per day as well as reduction in the intake of other B vitamins and protein, Berryman et al²⁷ observed symptoms of deficiency within fifteen to eighteen weeks. Supplementation with crystalline thiamine alone did not relieve these symptoms. Hathaway and Strom²⁸ found that 0.84 mg of thiamine per day allowed 3 women to live symptom-free and with a sense of well-being. Using the reaction-time technic, Tuttle et al²⁹ noted no aberration from normal unless the thiamine intake was less than 0.625 mg per day.

Values for the urinary excretion of thiamine at any given level of intake vary considerably among different observers, and there is an even greater variance of opinion in the interpretation of these results. Zero excretions of thiamine were observed at intakes of 0.5²⁷ and 0.61 mg per day¹⁴. On the other hand, other investigators²⁰ found some urinary excretion (10 to 29 gamma per day) of thiamine with intakes as low as 0.28 to 0.40 mg per day. When subjects ingested 0.7 mg of thiamine per day, Oldham et al²⁰ observed a sudden increase in the urinary excretion level to 35 to 78 gamma per day. At a daily intake of 0.84 mg,²⁸ the urinary excretion was 90 to 112 gamma per day. By some standards this value for urinary excretion is above the lower limits of "normal."

Alexander¹¹ was dissatisfied with the method of restriction of dietary intake for determining

minimal thiamine requirements. Instead, he made a thiamine balance study, which established a minimal thiamine requirement of 0.7 mg per day on a 2400-calorie diet, or 0.29 mg per 1000 calories if allowances were made for the urinary excretion of partial breakdown products of thiamine. Holt et al²⁰ employed a refinement of the urinary-excretion technic whereby increments of the thiamine intake were added and subtracted until a critical point of minimum urinary excretion was found. The higher excretion rate above this point was believed to represent a surplus above minimum physiologic needs. By this method the minimal thiamine requirement for adults was 0.6 mg per day, and that for infants was 0.14 to 0.20 mg per day.

A final biochemical approach to the problem of determining the minimal thiamine requirement was the use of a complex index based upon changes in blood lactic and pyruvic acids after glucose administration and exercise.³¹ Subjects with a daily thiamine intake of 0.4 mg were found to be at the borderline of biochemical abnormality. Probably, a lower level for the minimal thiamine requirement is obtained by this method because the pyruvic acid metabolism seems to remain constant even when the urinary-excretion level of thiamine has reached zero.¹⁴

In arriving at the value or values for minimal thiamine requirements, one must consider other factors. The generally accepted theory that an interrelation between carbohydrate intake and utilization of thiamine exists is questioned by Keys et al,¹⁴ who suggest that the actual thiamine requirement may be a constant as well as an amount proportional to the total fat calories and may be somewhat less than 0.61 mg per day, regardless of calories. This theory is opposed to the common idea that fat spares thiamine. It is unlikely that intestinal synthesis of thiamine plays a role in determining the minimal requirement because thiamine is not absorbed from the colon.^{11, 27, 32} Contrary to popular opinion that the demand for thiamine is increased during the consumption of alcohol, an isocaloric substitution of alcohol for carbohydrate resulted in increased thiamine excretion.³² This was interpreted as indicating a thiamine-sparing action of alcohol.

In a case of an American prisoner of war with severe beriberi, symptoms recurred when he was shifted from parenteral to oral vitamin therapy, but when hydrochloric acid was given in addition, he could be maintained fully on oral intake alone.³³ This observation is merely a clinical impression and is at variance with a better controlled study, which showed no effect of gastric anacidity on thiamine absorption as determined by the urinary excretion level.³⁴ Other experiments demonstrated that thiamine ingested with meals was excreted

is striking in view of the long period of maintenance at a given level of intake in one study and the brief period in the other. The lower values and steady decrease observed by Haines et al.⁵³ are difficult to reconcile with the results of the other two investigations.

Although these biochemical determinations prove a definitive relation between tissue saturation with vitamin C and the level of intake, there is difficulty in establishing the level below which subclinical deficiency occurs. A fasting plasma ascorbic acid level below 0.6 mg per 100 cc is considered by some to be the critical level necessary for normal vitamin C metabolism.⁵⁴ This would require an intake of approximately 50 mg of vitamin C per day. Moreover, plasma levels below 0.25 mg

development of tensile strength and healing in surgical wounds. The only dissenting report was that of normal healing of experimental wounds with a vitamin C intake of only 11 mg per day over an eleven-month period.⁵²

After considering these reports, I believe that a vitamin C intake of 30 mg per day is more than adequate to meet the minimal requirements in man except during periods of stress.

Fat-Soluble Vitamins

Vitamin D The minimal requirement for vitamin D in adults is approximately zero⁶¹; 400 I U of vitamin D is ample for children because this amount produces no greater calcium retention than 800 I U.⁴⁴ An increased demand for vitamin D has been shown in cases of steatorrhea.⁶⁴ Oral doses of as much as 12,000 I U of vitamin D per day may be insufficient to maintain calcium balance in steatorrhea, but the same quantity of vitamin D administered intramuscularly becomes effective.⁶⁵ There have been reports of rare cases in which the absorption of vitamin D was satisfactory but in which clinical rickets, resistant to the normal quantity of vitamin D, required 150,000 to 1,500,000 units daily for cure.^{66, 67}

Vitamin E The essentiality of vitamin E in human nutrition has not been established as yet. Although specific manifestations of vitamin E deficiency have been demonstrated in animals, no similar deficiency syndrome in man is known. Likewise, the human requirement, if there is one, has not been determined. Several series of measurements of the blood plasma level of vitamin E in normal human subjects show a range of 0.39 to 2.02 mg per 100 cc.⁶⁸⁻⁷⁰ Much lower plasma levels of vitamin E have been found in persons with malnutrition, sprue and impaired fat absorption.^{63, 70} The significance of decreased levels of vitamin E in the plasma is not known.

Vitamin K The minimal requirement for vitamin K is 1 mg per day or less. The quantity needed is usually supplied in sufficient amounts by the diet and by intestinal synthesis.^{44, 61} To prevent hemorrhagic manifestations in the newborn, it is advisable to give supplements of vitamin K to the mother during the last month of pregnancy.⁴⁴ When prothrombin deficiency occurs, as in cases of impaired intestinal absorption, 2 mg of vitamin K per day is more than enough to restore the prothrombin level to normal.⁷¹

Recommended Dietary Allowances

The National Research Council constantly reviews data derived from investigations into nutritional requirements, such as those surveyed above, and publishes revisions of recommendations for dietary allowances from time to time. In keeping with advancing knowledge about minimal requirements for vitamins, it is interesting to note the

TABLE 1 Relation of Daily Vitamin C Intake to Plasma Level

INTAKE mg/day	PLASMA LEVEL* mg/100 cc	PLASMA LEVEL† mg/100 cc	PLASMA LEVEL‡ mg/100 cc
22.3	—	0.26	—
33.0	0.48	—	0.25-0.36
33.0	—	—	0.42-0.63
37.0	0.72	—	—
62.5	—	0.75	—
70.0	—	—	0.50-0.86
78.3	—	0.87	—
82.0	0.93	—	—
107.0	1.05	—	—
400.0	—	1.20‡	—
437.5	—	1.49	—

*Data of Dodds and MacLeod.¹¹ A seven-day to ten-day adjustment period on each intake preceded these plasma values which represent two-day and six-day averages.

†Data of Johstoe et al.⁴⁴ The subjects were maintained for six to nine months at the various levels of intake.

‡Data of Haines et al.⁵³ The values recorded are those for the sixth week after the beginning of the various intakes which had been preceded by a saturation period. At each level of intake observed, there was a steady decrease in the plasma level during the six weeks of study.

§Determined after three days at an intake of 400 mg per day.

per 100 cc or intakes below 22 mg per day are believed to be in the deficiency range.^{54, 55, 59} Complete saturation of tissues and white blood cells with vitamin C was found to be accomplished by intakes slightly in excess of 70 mg per day,^{53, 59} but it has never been proved that complete tissue saturation is necessary for optimal health. In fact, as a result of saturation tests, it has been postulated that the body economy is more wasteful of its vitamins when they are in good supply.⁶⁰ When fully saturated, the body is estimated to contain $\frac{1}{4}$ gm of vitamin C.^{67, 69} Another approach, which has been introduced by Slobody et al.,⁵⁵ is the determination of tissue saturation with vitamin C by the rate of decolorization of dichlorophenol indophenol injections into the skin. As yet, its clinical application has not been tested.

A greatly increased demand for vitamin C in persons with burns and severe injury has been well demonstrated.^{36, 37} Experimental studies on wound healing in human subjects depleted in vitamin C⁶¹ have confirmed earlier observations^{67, 68, 69} of the need for additional vitamin C to promote

crease the difficulties of producing a state of experimental deficiency.¹⁷ The type of diet also alters niacin requirements. For example, tryptophane acts as a precursor for niacin,⁴⁶ whereas the probable presence of an antiniacin factor in corn would increase the need for niacin when corn products are ingested.⁴⁷

Determination of the urinary excretion of niacin or its metabolic derivative N-methyl nicotinamide has little value in establishing requirements for niacin. With intakes ranging from 6.9 to 25 mg per day in 12 subjects, the urinary excretion of niacin was found to be almost constantly 1.0 mg per day, and the fecal excretion 1.0 to 1.9 mg per day.²⁰ The N-methyl nicotinamide excretion in the urine was observed to be the same with intakes of either 12 or 22 mg per day.¹⁴

For lack of better data, the closest estimate to the minimal daily requirement for niacin is 5 mg, with an increase to 7.5 mg if there are corn products in the diet.⁴⁴

Lesser Known Members of the Vitamin B Complex

There are practically no data on the human requirements for the lesser known members of the vitamin B complex. Specific deficiency states for pyridoxine, pantothenic acid, para-amino benzoic acid, biotin, choline and inositol have not been discovered. Lack of folic acid and vitamin B₁₂ may contribute to the development of macrocytic anemias. It is most probable, however, that some of these lesser known or even some as yet unidentified components are essential to adequate human nutrition. This was demonstrated by experiments that showed incomplete recovery or even aggravation of some existing deficiency symptoms when depleted persons were given supplements of crystalline thiamine, riboflavin and niacin only. It was only after restoration of a full diet or addition of brewers' yeast that there was complete relief from all deficiency stigmas.^{24, 27}

The few scattered reports on lesser known members of the vitamin B complex are summarized as follows. The production of suggestive pyridoxine deficiency with manifestations of depression, mental confusion and leukopenia was reported to occur within two months on a synthetic diet containing supplements of the other known vitamins in crystalline or purified form, but the quantity of pyridoxine needed to "cure" was not determined.⁴⁸ The "burning-feet" syndrome described in a number of nutritional surveys of prisoners of war is attributed to pantothenic acid deficiency.^{24, 49} The possibility of pantothenic acid deficiency in man is questionable, however, on the basis of work that revealed excretions to approximate intakes ranging from 2.1 to 4.7 mg per day.²⁰ It is suggested either that no pantothenic acid is destroyed in the body or that intestinal synthesis compensates for the destruction in the tissues.²⁰ A study of human

utilization of biotin showed urinary and fecal excretion to be three to six times that of intake, the excess probably coming from intestinal synthesis.¹⁸ Consequently, human biotin deficiency is unlikely. On the basis of animal studies, the human requirement for folic acid is estimated to be 0.1 to 0.2 mg per day.⁴⁴ The hematologic response of patients with Addisonian pernicious anemia suggests that man requires less than 1 gamma of vitamin B₁₂ per day.⁵⁰

Any concern about meeting the human requirements for the lesser known members of the vitamin B complex can be allayed when it is known that the ordinary diet supplies these factors in adequate amounts when foods that contain the major components of the vitamin B complex are ingested.⁴¹

Vitamin C

In contrast with vitamin A and the B complex, the amount of vitamin C required to prevent clinical scurvy has been established with some accuracy,⁵² and several investigations have correlated the degree of tissue saturation with the quantity of vitamin C taken in.⁵³⁻⁵⁵

Investigators from the British Medical Research Council demonstrated, during an observation period of four hundred and twenty-four days, that a daily intake of 11 mg of vitamin C prevented the development of clinical scurvy.⁵² It is possible that an even lower level of intake would prevent scurvy because after 3 subjects had been on an 11-mg intake of vitamin C for one hundred and sixty days, they were maintained for one hundred and ninety-five days on intakes that were reduced still farther to 3.2 to 4.5 mg of vitamin C per day without the appearance of clinical signs of scurvy.⁵² In 6 cases of clinical scurvy developed during an intake of only 1 mg of vitamin C per day for seven months, 10 mg of vitamin C per day effected a slow cure after that period. It is interesting to note that the plasma levels of ascorbic acid fell with the same rapidity and to the same low levels of 0 to 0.05 mg per 100 cc both in the group whose daily intake was 1 mg of vitamin C and in the group that received 11 mg per day. Although 11 mg per day prevented the appearance of scorbutic manifestations, this intake of vitamin C did not eliminate such vague symptoms of deficiency as fatigue. To satisfy ill defined additional needs and to allow a margin of safety, it was suggested that a daily vitamin C intake of 30 mg be regarded as the requirement of a normal adult.⁵² This recommendation agrees with the League of Nations daily minimum requirement for vitamin C of 30 mg⁵⁶ and is close to the maximal daily utilization of 30 to 40 mg found by Crandon et al.⁵⁷

The correlation between plasma vitamin C levels and intake as found by different investigators is summarized in Table 1. The close agreement between the results of Johnstone et al.⁵¹ and Dodds⁵⁵

is striking in view of the long period of maintenance at a given level of intake in one study and the brief period in the other. The lower values and steady decrease observed by Haines et al.⁵³ are difficult to reconcile with the results of the other two investigations.

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50.0	—	—	0.42-0.63
57.0	0.72	—	—
62.5	—	0.75	—
70.0	—	—	0.50-0.86
78.5	—	0.57	—
82.0	0.93	—	—
107.0	1.05	—	—
400.0	—	1.20§	—
457.5	—	1.49	—

*Data of Dodds and MacLeod.⁴⁴ A seven-day to ten-day adjustment period on each intake preceded these plasma values which represent two-day and six-day averages.

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‡Data of Haines et al.⁵³ The values recorded are those for the sixth week after the beginning of the various intakes which had been preceded by a saturation period. At each level of intake observed there was a steady decrease in the plasma level during the six weeks of study.

§Determined after three days at an intake of 400 mg per day.

per 100 cc or intakes below 22 mg per day are believed to be in the deficiency range.⁵¹⁻⁵³⁻⁵⁹ Complete saturation of tissues and white blood cells with vitamin C was found to be accomplished by intakes slightly in excess of 70 mg per day,⁵³⁻⁵⁹ but it has never been proved that complete tissue saturation is necessary for optimal health. In fact, as a result of saturation tests it has been postulated that the body economy is more wasteful of its vitamins when they are in good supply.⁶⁰ When fully saturated, the body is estimated to contain 4 gm of vitamin C.⁵⁷⁻⁵⁹ Another approach, which has been introduced by Slobodov et al.,⁵⁸ is the determination of tissue saturation with vitamin C by the rate of decolorization of dichlorophenol indophenol injections into the skin. As yet, its clinical application has not been tested.

A greatly increased demand for vitamin C in persons with burns and severe injury has been well demonstrated.³⁶⁻³⁷ Experimental studies on wound healing in human subjects depleted in vitamin C⁶¹ have confirmed earlier observations⁵⁷⁻⁶²⁻⁶³ of the need for additional vitamin C to promote

downward trend of recommendations in the latest 1948 National Research Council revision.⁵¹ The specific vitamin allowance recommendations for those vitamins for which definite deficiency states have been recognized are summarized as follows

Vitamin A—5000 I U per day, 8000 I U per day during lactation

Thiamine—10 mg per day for sedentary persons to 18 mg per day for those doing heavy labor

Riboflavin—15 to 18 mg per day, 30 mg per day during lactation

Niacin—12 mg per day for sedentary life to 18 mg per day for heavy labor

Vitamin C—70 to 75 mg per day, 150 mg per day during lactation

Vitamin D—400 I U per day during childhood, adolescence, pregnancy and lactation, minimal amounts for adults generally

Vitamin K and folic acid are recognized, but no quantitative recommendations are made

The report points out that food supplying adequate thiamine, riboflavin and niacin will inherently supply sufficient quantities of the remaining components of the vitamin B complex.⁵¹ In my opinion, this statement constitutes a strong argument for utilizing food to combat deficiency states and for eliminating the use of crystalline, synthetic or purified vitamin supplements, which cannot contain all nutrients in balanced quantities

In discussing these recommended dietary allowances, Jeans⁴⁴ emphasizes that they are not in any way a yardstick of requirements, but are definitely above average requirements, sometimes reaching twice the minimum. The allowances are a goal for ensuring good general nutrition, but "persons ingesting less than the allowances are not deficient *ipso facto*"⁴⁴

It is my opinion that many claims that the American diet is inadequate are based upon use of the National Research Council's recommended dietary allowance, as if the levels appearing there were minimal requirements rather than above average. Jeans believes that the over-all American dietary intake is much more sufficient in the vitamins than is often stated

Such a lengthy review of recent data about minimal requirements seems justified because they are the foundation for evaluating the adequacy of diets. If food intake does not supply the minimal requirement of essential vitamins, supplements are justified. If, on the other hand, dietary intakes meet the minimal requirements, supplements are of little value, unless they cause an improvement in health and well-being beyond that resulting from an unsupplemented diet. These two alternatives will be examined in the next section of this review

(To be continued)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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CASE 35501

PRESENTATION OF CASE

A seventy-year-old man was brought to the Emergency Ward in shock by the Fire Department.

He was feeling relatively well until one and a half hours prior to entry, when he suddenly collapsed while waiting in the office of his physiotherapist. A physician found the patient cold and clammy and sweating profusely without obtainable pulse or blood pressure. Oxygen was given, and tourniquets were applied to the legs. Soon afterward he regained consciousness and stated that no pain preceded this episode.

Twelve years prior to admission he had a cerebrovascular accident from which a mild left hemiparesis remained and since that time his blood pressure averaged 220 systolic, 140 diastolic. Seven years before entry he suffered a myocardial infarction and was treated at a community hospital. His recovery was complete as confirmed by an electrocardiogram made six months before entry. This showed normal rhythm at a rate of 70, left-axis deviation, normal PR and QRS intervals, small upright T waves in the limb leads and upright T waves in the precordial leads. For the past twelve years he had led a quiet life and at no time complained of symptoms of congestive failure or hypertension. One month prior to entry he developed a generalized muscular achiness that was somewhat improved by physiotherapy.

Physical examination revealed a very pale, cold, sweaty, moderately obese man in profound shock but not unconscious. There was no cyanosis of the face or distention of the neck veins. The pupils were constricted but reactive. The lungs were clear except for a few moist basal rales. The heart was not grossly enlarged, and the sounds were barely audible but regular. There was no gallop and no murmurs. The abdomen was prominent, soft and hyperresonant in the left upper quadrant. There was moderate tenderness beneath the left costal

margin and a firm fullness over the descending colon, but no obvious masses were felt. There was no ankle edema. The legs were cold, pale and pulseless.

Neurologic examination showed a slightly increased muscular tone of the left arm over the right, and the spontaneous arm movements were easier on the right than the left. The reflexes were not remarkable except for a decreased response of the left knee jerk.

The temperature was 99°F, the pulse 90, and the respirations 22. The blood pressure was 95 systolic, 75 diastolic.

Urinalysis revealed no abnormalities except for a +++ test for albumin. Examination of the blood disclosed a white-cell count of 28,700, with 82 per cent neutrophils, 15 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The hemoglobin was 11.5 gm per 100 cc. (three weeks prior to this determination it was 14 gm). The nonprotein nitrogen was 49 mg per 100 cc and the prothrombin time was 15 seconds (normal, 15 seconds). An electrocardiogram showed sinus tachycardia at a rate of 110 with a PR interval of 0.17 second and a QRS interval of 0.08 second. There were prominent Q waves in Lead 2, 3, and AVF. The T waves were flat in Lead 2 and V₁, inverted in Lead 3 and AVF and upright in the other leads. Another electrocardiogram taken on the second hospital day disclosed normal rhythm at a rate of 95 to 100 with moderate left-axis deviation, inverted T wave in Lead 1 (for the most part late), flat T wave in Lead 2, and slightly elevated ST segment and deep Q₁ wave in AVF. The precordial leads showed low T waves with slightly late notched TV₄, and late inversion of the T wave in V₆.

Shortly after admission the patient improved. The blood pressure rose to 110 systolic, 95 diastolic, and the pulse became more firm, however, he remained in shock. Because of persistence of collapse four hours later a slow blood transfusion was administered, after which he became rested and slept quietly. On the second hospital day the patient awoke lucid, appearing dramatically improved, but the blood pressure remained low—100 systolic, 80 diastolic. The hemoglobin had decreased to 9 gm, and the white-cell count to 19,800. He complained of aches all over when moving and mentioned that his "bowels hurt."

On the third hospital day he was restless and disoriented, and he suddenly began to breathe heavily and went into shock, the blood pressure and pulse became unobtainable, and shortly thereafter he died.

DIFFERENTIAL DIAGNOSIS

DR ROBERT S PALMER* When a person faints, one cannot say right off whether or not it is benign

*Associate physician, Massachusetts General Hospital

fainting When fainting occurs in an elderly man whose subsequent course excludes fainting of the benign or transient sort, many people think of myocardial infarct, and so do I. In elderly persons particularly myocardial infarction may be without pain and may be heralded by syncope. Although it is unusual, sudden collapse may happen at the onset in cerebral hemorrhage, and also may be caused by overwhelming infection, an acute condition of the abdomen, or internal hemorrhage. This man's blood pressure was not the ordinary wide-pulse-pressure type seen in hypertension of the elderly, which we think is due to large-vessel sclerosis. The diastolic pressure was elevated and may have been due to chronic vascular nephritis. I have here the electrocardiogram taken seven years before entry, a feature of which is a high ST segment in Lead 3, with late inversion and elevated ST segment in Lead 2. If the clinical course were characteristic I should think we might accept the given diagnosis of posterior myocardial infarction at that time. Recovery seemingly was satisfactory, and an electrocardiogram made six months before entry had returned to normal in respect to T-wave changes. Coming back to the conditions that can cause shock, I wonder about an acute condition of the abdomen and hemorrhage. From the physical signs given here, I can see nothing that really helps me definitely to rule abdominal disease in or out. When a patient is in profound shock, of course, the signs of an acute condition of the abdomen are equivocal.

The neurologic examination suggests the residua of an old cerebral thrombosis. In summary, the background of this patient, admitted in profound shock, is one of arterial hypertension with diffuse vascular disease cerebral, cardiac and renal.

Do the laboratory data help to settle the differential diagnosis of shock due to myocardial infarction, overwhelming infection, acute abdomen or hemorrhage? The white-cell count of 28,700 was high for shock and for hemorrhage, it was not too high for an overwhelming infection. It was rather high for myocardial infarction. The hemoglobin was definitely lower than three weeks earlier. Could he have lost 2.5 gm of hemoglobin from shock alone, or was it an indication of hemorrhage and shock in a person who had lost enough blood so that he did not concentrate since ordinarily in a shock state one expects hemoconcentration? The nonprotein nitrogen of 49 mg per 100 cc, perhaps slightly elevated, may have been a manifestation of shock, although it possibly was related to chronic vascular nephritis. The admission electrocardiogram, which I have here, is the usual complete tracing and should help us.

In Lead 3 there is a suggestion of elevated ST segment and definite late inversion of the T wave, and in the precordial lead there is low QRS voltage and a low T wave. Previously we did not have

unipolar limb leads nor a precordial lead in the sixth position, but we know from the previous electrocardiogram at least that the T wave in the conventional third lead was low upright, whereas it was inverted on this one later tracing. This would be consistent with the expected change of a posterior myocardial infarction. The second tracing, taken on the next day, showed in addition a rather depressed ST segment in Lead 1 and late inversion of the T wave. In Lead 3 the T wave is now upright, which is disturbing if we are thinking of posterior or basal infarction. There are slight changes in the unipolar limb leads, which may be seen in posterior or basal infarction. The sixth precordial lead shows an additional change. There is quite good QRS voltage, with late inversion of the T wave. It is far enough out so that it may be close to but not directly over an area of infarction at the base of the left ventricle.

Regarding progress while the patient was in the hospital, blood was given. Transfusion is good therapy for shock and not infrequently may be indicated in the shock of myocardial infarction. The hemoglobin was still lower on the second hospital day. If we can trust the laboratory determinations, this patient had lost about a third of his hemoglobin. The white-cell count was now 19,800. I do not know what the "aches all over" represented and whether or not they were connected with the same complaint of a month prior to admission. I find nothing specific enough in the statement that his "bowels hurt" to help me.

This elderly man with hypertension and cerebral, cardiac and renal sclerosis had suffered an old posterior or basal myocardial infarction and a cerebral thrombosis with a left hemiparesis. When a person is found in shock, and the shock persists, there is no way of telling from the signs whether or not shock was due to a heart condition, an acute overwhelming infection, rupture of a hollow viscus or hemorrhage. The appearance and indeed the symptoms of these different conditions sometimes cannot be told apart. He may have had another attack of coronary thrombosis, and if so, from the diffuse changes in the electrocardiogram, it must have been a large one. Could he have had an acute condition of the abdomen? There was no sign of peritoneal irritation and nothing to indicate ileus, and there was nothing in the past history to suggest ulcer or gall-bladder disease or anything that would make us think that he had a rupture of a hollow viscus. Did he have internal hemorrhage? I have been fooled by an elderly person who I thought was having a mild attack of coronary insufficiency, and subsequently was proved to have had hemorrhage into, of all things, a hepatoma, which was quite large. Did this patient bleed into the gastrointestinal tract? In my experience a person of middle age or older who has a known ulcer and who is known to be bleeding and dies in uncontrollable

shock sometimes proves to have had a silent myocardial infarction. If this patient had gastrointestinal bleeding we should have seen or heard of blood at one end or the other of his intestinal tract. It is still conceivable that he may have bled somewhere, which is not apparent to me from the data at hand.

Let us see where we stand. Did he have a coronary thrombosis? Somewhat against this diagnosis is the syncope but it is not too unusual, especially in an elderly man. He did not have pain. At least when he became conscious he said that he had no pain. Again this is unusual but does not exclude the diagnosis. He had a very high white-cell count—higher than in most cases of myocardial infarction, let us say. The electrocardiographic picture is not complete enough for me to be actually sure of a diagnosis, perhaps because he did not live long enough to develop the complete pattern. Perhaps the exploring electrodes were near but not directly over dead muscle. Did he have hemorrhage? The high white-cell count and the loss of one third of his hemoglobin are in favor of hemorrhage. A hematocrit and other blood studies would have helped since I do not like to depend on the hemoglobin determinations alone. Since we have nothing to point to an acute overwhelming infection or peritonitis and since we do not know where he bled, I am inclined to discard these possibilities and to suggest that he had extensive myocardial infarction, posterolateral or posterior, perhaps involving the septum extensively.

DR BERNARD JACOBSON: When he entered the Emergency Ward, examination revealed nothing in the rectum, and the small bit of stool that was obtained was brown and guaiac negative.

DR PALMER: That is evidence against hemorrhage into the gastrointestinal tract. What would happen if a person ruptured the ventricular septum, I do not know. Did he die of ventricular fibrillation? If he had extensive old myocardial disease and an additional fresh infarction he may have had ventricular fibrillation, and no specific immediate cause for death was found. Finally, did he have overwhelming pulmonary embolism? He was an old man, who had been in bed three days in profound shock, not moving very much, and he had had tourniquets on all four extremities. I think he may have had a pulmonary embolism as a final episode.

A PHYSICIAN: If this were a gastrointestinal hemorrhage, could the shock produce changes that would be consistent with these electrocardiograms?

DR PALMER: It's a wonderful suggestion. If he was anemic and his hematocrit was low he would have very few red cells circulating. That might cause myocardial ischemia and alteration in the electrocardiogram. I do not know, but I suppose it could cause such electrocardiographic changes

and therefore might be misleading. I think that is a good point.

DR SAMUEL GOLDFARB: Do you suppose the hemoglobin levels are correct? This man had a hemoglobin of 14 gm before his accident and 11.5 gm on admission, going down to 9 gm the next day, without taking into consideration that he probably received 500 cc of blood. How often do we see myocardial infarction produce rapid and sudden loss of hemoglobin?

DR PALMER: I do not know whether it could happen. I think hemoglobin values alone are doubtful but since the hemoglobin went from 14 gm to 11 gm and then down to 9 gm it almost makes me think something like that has happened.

A PHYSICIAN: Could aneurysm rupturing the septum occur without pain?

DR PALMER: I suppose it could, though I do not know.

DR JACOBSON: There is a slight correction to the record. I saw the patient at a physiotherapist's office downtown and found him completely unconscious in profound collapse, and I want to pay tribute to the Fire Department of the City of Boston for the prompt arrival of oxygen in one minute flat. I transferred him here as soon as possible. The statement is made that as soon as he regained consciousness he said he had no pain. He was unconscious when I saw him at quarter to two in the afternoon and he remained unconscious until seven o'clock the following morning. Thereafter he complained of slight tenderness on palpation of the left lower abdomen.

A PHYSICIAN: It was mentioned that the pulsations in the legs were absent on one examination. Did that come back or remain absent?

DR JACOBSON: The dorsalis pedis and posterior tibial pulsations had been absent for the past year or more.

DR GOLDFARB: Is this history compatible with dissecting aneurysm?

DR PALMER: I suppose dissecting aneurysm could occur without pain. I have known of one patient, a man in the Home for Aged Men with no history of pain, but when he died of something else, the evidence of former dissection was found.

DR JACOBSON: Dr Bland saw the patient on entry to the hospital. We were worried about the 11.5 gm of hemoglobin in a patient with hemocrit concentration of shock. During the following fourteen hours we were considerably worried by the fact that the left abdomen seemed a little tense and the patient winced when we touched it. On the following day when he was conscious his left abdomen was still a little tender but not spastic. No masses were felt. I also might add that he began to urinate eight or nine hours after he entered the hospital and that the urinary output thereafter was adequate.

DR PALMER: That would go with shock.

CLINICAL DIAGNOSES

Arteriosclerotic heart disease
 Infarction of myocardium, due to arteriosclerotic coronary thrombosis

DR PALMER'S DIAGNOSES

Myocardial infarction, extensive, recent
 Old posterior myocardial infarction
 Hypertension, with diffuse vascular sclerosis
 Old cerebral thrombosis

ANATOMICAL DIAGNOSES

Arteriosclerosis, generalized, with ruptured arteriosclerotic aneurysm of abdominal aorta
 Retroperitoneal hematoma, massive
 Infarct of heart, old
 Infarct of cerebellum, old
 Hypertrophy of heart
 Nephrosclerosis



FIGURE 1

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: Autopsy showed that the falling hemoglobin was the key to this case. We found on opening the peritoneal cavity that

the retroperitoneal tissues on the left side of the abdomen way down into the pelvis were filled with clotted blood. This was the result of rupture of a saccular arteriosclerotic aneurysm of the aorta, which lay just above the bifurcation (Fig 1). The clot showed evidence of layering, and I think he must have had several episodes of bleeding at various times. The other findings were merely those of long-standing hypertensive heart disease and severe arteriosclerosis, shrunken kidneys, hypertrophied heart with an old completely healed posterior infarct and marked atheroma of the vessels of the circle of Willis, with a small area of softening of the cerebellum. The extraordinary thing about the story is the lack of obvious pain. Dissection of large amounts of blood through the retroperitoneal tissues in my experience almost always has been associated with the most intense pain. Probably his mental clouding had a good deal to do with the fact that he did not complain of this.

CASE 35502

PRESENTATION OF CASE

A sixty-nine-year-old widow entered the hospital because of extreme weakness for about one year and jaundice for about one month.

The patient dated the onset of poor health from an operation for ruptured appendix followed by peritonitis and drainage at the age of thirty-five. A postoperative ventral hernia was repaired but recurred. At the age of forty-four she received the diagnosis of "pernicious anemia" while seeing a doctor for reasons she did not remember. For this she was urged to eat raw liver, which she was unable to do because of vomiting; injections were discontinued because they were painful, "copper and iron" tablets were taken. She had not had antianemia treatment for years. A subtotal thyroidectomy was performed at the age of sixty-three for "toxic goiter." Radiograms at another hospital at the age of sixty-seven showed an enlarged heart, an electrocardiogram disclosed auricular fibrillation, left bundle-branch block and left ventricular strain. Although she had not considered herself in good health for "many" years, the patient noticed that her usual weakness became more pronounced six months before entry, following the death of a son; anorexia likewise appeared and increased. During this time her weight had decreased from 178 to 158 pounds (several years previously she had weighed 240 pounds but had not tried to reduce). During the four weeks before entry her attention had been called to the gradually increasing yellowish discoloration of her skin, which had steadily progressed. Itching of the skin over the arms and anterior chest was present during the first week of jaundice but then abated. This was not accompanied by pain, clay-colored stools, nausea, vomiting or fever.

The urine was noted to be darker than usual. There was no previous episode of jaundice, no change in bowel habits or stools and no history of exposure to jaundiced persons, chemicals or transfusions. She did not drink alcohol.

Physical examination revealed a moderately icteric woman, lying in bed in moderate distress as evidenced by rapid, forced respirations. Moderate palmar erythema was noted. No spider angiomas were present. The scleras were icteric. The chest was emphysematous, moist rales were present at both bases, more marked on the left. The heart was enlarged, the point of maximal impulse being 2 cm left of the midclavicular line. The rhythm was irregular. The sounds were of good quality, the pulmonic second sound was markedly greater than the aortic, a Grade II, rough systolic murmur was best heard at the lower sternal border. The abdomen was obese. A large ventral hernia occupied the left lower quadrant. The liver was palpated 11 cm below the costal margin in the midclavicular line, the edge was firm, sharp and nontender. The splenic tip was questionably palpable. A ++ pitting edema was present over the lower two thirds of the leg and the sacrum. The knee jerks and ankle jerks were absent, vibratory sense was absent in both ankles and the right knee.

The blood pressure was 92 systolic, 48 diastolic. The temperature was 100°F, the pulse 96, and the respirations 28.

The blood showed a red-cell count of 3,820,000, with a hemoglobin of 10.8 gm. The white-cell count, was 7600, with 88 per cent neutrophils, and later ranged between 12,000 and 16,000. Urinalysis revealed a + test for albumin, and bile. The fasting blood sugar was 124 mg per 100 cc, the sodium 133.9 milliequiv, and the chloride 101 milliequiv per liter. The total protein was 5.6 gm per 100 cc, with an albumin-globulin ratio of 3.3/2.33. The nonprotein nitrogen was 20 mg per 100 cc, and the alkaline phosphatase 12.9 units, reaching 22.3 units on the eighteenth day. The prothrombin time was normal on admission and only slightly elevated later. The van den Bergh reaction was 8.7 mg per 100 cc direct, 13.2 mg indirect. The amylase was 33 units per 100 cc, the cephalin-flocculation test was + in twenty-four hours, ++ in forty-eight hours and, twenty days later, +++ in twenty-four hours and ++++ in forty-eight hours. The cholesterol was 139 mg and the cholesterol esters 54 mg per 100 cc, the thymol flocculation was negative, the thymol turbidity 2.10 units, the urine urobilinogen 3.0 to 7.3 Ehrlich units, and the stool urobilinogen normal. The stools were guaiac negative, and cultures were negative for pathogens. A heterophil-antibody test was negative. The blood culture was negative. The clotting time (without tube) was 9 minutes, and the bleeding time (ear puncture), 1 minute. A bone-marrow aspiration revealed a slight shift to the left in the myeloid and also in the erythroid

series, no megaloblasts or other abnormal cells were seen. An electrocardiogram revealed auricular fibrillation, at a rate of 100, a QRS complex of 0.12 second, low to absent R wave in Lead V₁ and V₄, and left bundle-branch block. A gastric aspiration on the fifth hospital day failed to reveal any free acid, but "pure bile" was present.

Radiographic studies showed left ventricular and left auricular enlargement. The aorta was tortuous and calcified. The right leaf of the diaphragm was elevated but on fluoroscopic examination moved as well as the left. Hepatomegaly and splenomegaly were prominent features. A barium enema was unsatisfactory because of the patient's inability to retain sufficient barium, however, diverticula were demonstrated in the sigmoid region, and the cecum was high-placed. A gastrointestinal series revealed no esophageal varices. A small hiatus hernia was present. No intrinsic abnormality of the stomach, duodenal bulb or duodenal loop was present. The duodenal loop was not enlarged. A small-bowel series was not remarkable, except for one segment of atonic bowel on the three-hour film. It was also noted that the bones were atrophic with fairly marked degenerative changes.

A sigmoidoscope was passed to 13 cm, with great difficulty. The bowel was very spastic and was intensely hyperemic.

The temperature remained elevated in irregular fashion, reaching 104°F on the first, sixth and seventh hospital days, dropping to 99°F and below on the eighth and ninth days, and becoming elevated again, gradually reaching 104°F on the fourteenth day, normal on the fifteenth day and up to 104°F again on the twenty-second and twenty-third days. Although the patient was reluctant to take food and refused to force fluids, she was kept well hydrated, and the caloric intake increased by frequent prompting. It was noted on one occasion that appetite increased, and the patient was subjectively better coincident with a high rise in temperature. Therapeutic measures consisted mainly of Digitoxin, 0.15 mg daily, Crysticillin, 300,000 units daily, Hykinone, 4.8 mg daily, and dihydrostreptomycin, 1.0 gm daily, as well as supportive and antipyretic measures. Mercurhydrin was given on occasion. The patient's general condition grew steadily worse. On the fifteenth hospital day abdominal distention had become an increasingly prominent feature, being only somewhat relieved by enemas and stupes.

A liver biopsy on the twenty-first day was reported as follows:

The portal areas show increase in the number of small-bile ducts and a moderately severe inflammatory reaction in which polymorphonuclears are numerous. Small cholangioles are dilated, and there are foci of pseudotubular change in the liver cords. Two foci of necrosis and degeneration of liver cells are seen. No inspissation of bile in the cholangioles or canaliculi is seen, and there is no bile pigmentation in the liver cells. The findings nevertheless suggest obstruction in the extrahepatic biliary tract.

On the twenty-fifth day it was noted that the jaundice had deepened, and the liver edge was only 4 cm below the costal margin. Stupor increased, and the patient died quietly, without change in the vital signs, on the twenty-sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR ALFRED L. DUNCOMBE* May we see the x-ray films?

DR STANLEY M. WYMAN The film of the chest taken in the upright position shows the heart to be considerably enlarged to the left probably in the region of the left ventricle. The tortuous, calcified aorta is well seen, and also the elevation of the right leaf of the diaphragm. This appears to be rather localized anteriorly and probably represents localized enlargement of the liver in this region. The spleen is greatly enlarged extending down to the crest of the ilium, and there are a number of round calcific shadows overlying the spleen suggesting phleboliths in the spleen itself.

The kidney shadows are not adequately seen on any film, but they may be small. One film of the attempted barium enema shows nothing remarkable except for diverticula in the sigmoid. The films from the gastrointestinal series show some pressure on the lesser-curvature aspect of the stomach, with depression of the duodenal bulb downward. This is well seen in the spot film. The esophagus itself is quite well demonstrated, and there is no evidence of varices. There is no evidence of pressure on the second portion of the duodenum in its medial aspect. The stasis in the small bowel, I think, may be accounted for by the patient's large hernia, which is seen at this point.

DR DUNCOMBE Will you comment on the barium swallow?

DR WYMAN It outlines an essentially normal esophagus, which is pushed backward by the enlarged heart.

DR DUNCOMBE The problem is that of a woman with painless jaundice of a number of weeks' duration, following a period of increasing poor health, which went on to a rather rapidly fatal termination.

There are several things in the past history that should be mentioned and disposed of. The diagnosis of pernicious anemia was made twenty-five years before admission — incidentally, that was two years ahead of the publication of Dr Minot's paper. Perhaps it is an error in the history. She probably did not have pernicious anemia at any time. Her blood picture was not that of pernicious anemia and the bone-marrow biopsy did not show the findings of pernicious anemia. She had a toxic goiter removed six years previously, with weight loss of some 50 or 60 pounds since that time. The possibility of recurrent thyrotoxicosis should be considered, but there is no other evidence for it.

Then she was known to have had heart disease of some type for a few years. The heart was enlarged

chiefly in the region of the left ventricle. She was fibrillating. There was no history of hypertension. Her blood pressure in the hospital was low — 92 systolic, 48 diastolic. The electrocardiogram is of no value in the diagnosis of the heart disease but confirms the presence of fibrillation. She had a relatively loud systolic murmur heard best at the lower border of the sternum. This murmur is consistent with disease of the aortic valve in a person who has developed failure and a fall in blood pressure and is acutely ill. I think it most likely that the autopsy showed disease of the aortic valve and a large left ventricle.

Is it possible that the heart disease was a major factor in her present hospital admission? It seems unlikely. She had a fever. She went downhill rapidly. The blood culture was negative. It seems unlikely that subacute bacterial endocarditis should be seriously considered. Disposing of the three things in the past history we have to consider the problem of painless jaundice at the age of sixty-nine. Perhaps the most important of the x-ray findings is the presence of a large spleen. This was questionably palpable, but the x-ray examination confirms that there was a large spleen. Dr Jones said earlier this morning at Medical Grand Rounds that a large liver and large spleen in the presence of jaundice means that there must be intrinsic liver disease, and not obstructive jaundice. Extrahepatic obstruction should not give this large spleen.

Before dismissing the possibility of biliary obstruction, one would have briefly to consider carcinoma of the head of the pancreas and carcinoma of the bile duct or of the ampulla of Vater with resultant damage to the liver. Against carcinoma of the ampulla of Vater is the absence of a positive guaiac reaction in the stool. The majority of cases should have blood in the stool. Certainly, a common-duct stone can produce jaundice, a large liver and intermittent fever and can go on to a fatal termination without any significant degree of pain, but we have already concluded from the presence of a large spleen that the primary difficulty was within the liver.

What type of liver disease could she have had that would end up with this clinical picture and fatal termination? There was no history that suggests the usual etiologic factor in producing alcoholic cirrhosis. Apparently, the patient had been a neurotic type of person. She may well have had a poor diet, but she certainly was not alcoholic. The possibility of biliary cirrhosis should be considered. The usual term "Hanot's cirrhosis" is confusing. It apparently has been a catch-all for a number of poorly understood conditions. In recent years it has been shown that following virus infections of the liver, chronic hepatitis, progressing to a type of biliary cirrhosis that is consistent with this clinical picture, can develop.

The laboratory findings, as so often happens in the presence of jaundice, are confusing. At least they are to me. She had bile in her stools because

*Assistant in medicine, Massachusetts General Hospital

they were not clay colored on admission, and there is no mention of clay-colored stools later on. She had normal urobilinogen in the stools and only moderately elevated urobilinogen in the urine. This indicates that there was not a high degree of extrahepatic obstruction. The alkaline phosphatase, being moderately elevated and rising, is suggestive of extrahepatic obstruction. The cephalin-flocculation test was strongly positive, suggesting a considerable degree of liver damage. The cholesterol was very low, as were the cholesterol esters. These indicate severe hepatic damage rather than extrahepatic obstruction.

I am sure the problem on the ward was whether this was extrahepatic or parenchymatous jaundice. Finally, a biopsy was done, which I do not believe can completely answer the question. There was evidence of proliferation of the small bile ducts and an inflammatory reaction, but inspissation of bile in the cholangioles that would ordinarily be seen in extrahepatic obstruction was not present. However, to the pathologist, the findings suggested obstruction in the extrahepatic biliary tract. In spite of that, I believe that the primary difficulty must have been within the liver and that she had some type of cirrhosis, probably biliary cirrhosis.

The other problem is the high, localized elevation of the diaphragm, which raises the question whether this woman had developed a hepatoma. The biopsy did not show it, but it could well have been missed and I think the pathologist is the only one who can answer that.

A PHYSICIAN: Does the fact that the liver border went down from 11 cm to 4 cm mean anything to you?

DR DUNCOMBE: I think that it suggests an acute or subacute infection of the liver with cirrhotic changes of the type that has been described following virus infection.

A PHYSICIAN: Would you comment on the peculiar fever that this woman ran?

DR DUNCOMBE: There was some statement here that meant nothing to me. It was noted on one occasion that her general sense of well-being and appetite improved with the high fever. People with severe liver disease and particularly people with cancer in the liver can have a high, irregular, septic temperature, and I assume that it is on the basis of severe liver disease, possibly with a hepatoma.

DR RICHARD J CLARK: Would you consider cholangitis in itself as possibly being the background?

DR DUNCOMBE: Whatever the terminal illness causing jaundice of six weeks' duration, some difficulty had been present for some months previous to that period. I do not see how one can rule that in or out completely.

DR TRACY B MALLORY: The discharge diagnosis from the wards was subacute atrophy of the liver. I wonder whether there is anyone who wishes to defend that?

DR BENJAMIN CASTLEMAN: I believe they made that diagnosis because the liver shrank so rapidly. At least the same examiner thought so.

CLINICAL DIAGNOSES

Subacute yellow atrophy of liver
Arteriosclerotic heart disease

DR DUNCOMBE'S DIAGNOSES

Biliary cirrhosis of liver, probably secondary to virus hepatitis
Aortic stenosis
Hypertrophy, left ventricle

ANATOMICAL DIAGNOSES

Cholelithiasis
Fistula, cystic duct to duodenum
Obstructive biliary cirrhosis
Splenomegaly, Banti type
Cardiac hypertrophy

PATHOLOGICAL DISCUSSION

DR MALLORY: At autopsy we found that the liver certainly could not have shrunk much in size because it was still very large, weighing 2520 gm. The apparent shrinkage was due essentially to elevation of the diaphragm.

A large gallstone was found in the common bile duct just above the ampulla, an adequate cause for the development of an obstructive biliary cirrhosis. With further dissection we found that the biliary tree had spontaneously drained itself, that the gall bladder had become a narrow tube with thick fibrous walls but that the cystic duct was dilated to equal diameter and a fistula had developed between the cystic duct and the duodenum. Evidently, drainage had been re-established after a very prolonged period of obstruction of the common duct. At the time of autopsy the inflammatory infiltration in the liver had become more impressive than it was in the biopsy. Either it had extended or perhaps the biopsy was not representative. The surface of the liver was quite finely granular, and the tissue was very firm, and cut with a great deal of difficulty.

The spleen was very large, weighing around 800 gm, and showed on microscopical examination minimal but, I believe, distinct changes suggesting portal hypertension. This is the Banti type of spleen, something that is very rarely seen with a biliary cirrhosis, only with one of very long standing.

The heart was much enlarged, weighing 600 gm, and we could find no reason for it other than an accumulation of a great deal of pericardial fat. There were no valvular lesions, no coronary-artery narrowing, no myocarditis and no evidence that the patient had ever had hypertension. Although heart disease must have been present, I cannot give it a name and say what kind it was.

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HOLIDAY

THE holiday nearest to the hearts of the western world comes opportunely at a time when practically everyone needs a rest after the weeks spent in arduous preparation for Christmas. Unfortunately the long-anticipated day has itself become so exhausting that a second holiday is necessary a week later to recover from the observance of the first—were this provision not rendered ineffective for many by the necessity of dedicating New Year's Day to the task of recovering from the indiscretions of New Year's Eve.

The traditional festival season is long anticipated and unmistakably merry but something of an ordeal.

After all, as some astute philosopher has suggested, it is not so much a rest that man needs in his holidays as it is a change of direction, and this the major festival season of Christianity provides, not only in the intellectual and some of the physical habits of man, but in his point of view as well.

Man is essentially a materialistic being who suspects that in concrete possessions he may find peace and contentment. And still he knows, when he stops to consider it, that nothing is farther from the truth. More radios, more amusements, more automobiles and other faster and more potentially lethal forms of transportation go parallel with more unhappiness, more broken homes, more crime and an increasing loss of true moral values. Those who link their hopes of happiness to ownership are doomed to frustration. Man enters the world naked, it has been said and naked he leaves it, an observation that has frequently been confirmed in the silent watches by many a family doctor.

With the extremes of poverty and wealth of discomfort and comfort, of misery and luxury that exist in the world today greater than ever before, and a general lack of that security that cannot be purchased, it becomes apparent that some other type of currency must be used that is available to all, in the purchase of human peace and understanding.

Coldly scientific or blindly emotional as man may be, still the only currency he can use that cannot be depreciated is one that is measured in spiritual values only.

With which the *Journal* wishes its readers a Merry Christmas, replete with candy canes, and a Happy New Year equipped with flexible but shatterproof resolutions.

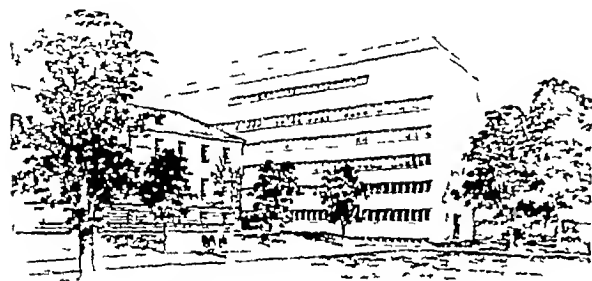
MASSACHUSETTS GENERAL HOSPITAL LOOKS AHEAD

THE spirit of research has prevailed at the Massachusetts General Hospital since the founding of the hospital, whose time-honored contributions to medical progress in the nineteenth century are too well known to need reciting. In the first half of the present century also clinical research at the hospital has grown apace. Research laboratories have been set up in every nook and cranny of the Bulfinch Building, and in 1939 a suite of research laboratories was made available for the surgeons with the opening of the White Building.

In 1942 Harvard's Huntington Laboratory moved to the hospital and was given an entire floor in the

old domestic building, where converted kitchens and dining rooms lent themselves well, although far from perfectly, to research purposes. Ultimately most of this building will be devoted to laboratories. The most recent acquisitions of research laboratory space are for the Pediatric and Gynecological services in the Burnham-Vincent Building, which was opened in 1947, and for the Dermatological Service in what was once Ward E and the old Bradley operating theater.

But even this is not enough. Since the last war funds for research have become available to a



RESEARCH BUILDING

degree undreamed of a decade ago, creating increased opportunities to put investigators to work. These workers on their part have been flocking to the Massachusetts General Hospital in ever-increasing numbers from all parts of the earth.

A building devoted exclusively to research became essential, and at long last there is to be one, with the erection of a six-story structure along the Blossom Street edge of the hospital's property, beginning at the corner of Allen Street, where the Director's house now stands. This house must be abolished, which may cause some regret, but progress demands the sacrifice. There was no other convenient place to put the new building.

Acceding gladly to public need, the hospital will devote major research activities in the new space largely to investigations on cancer, cardiovascular disease and arthritis, with one floor utilized exclusively for the most fundamental type of biochemical research — enzymology — under the direction of the world-famous Dr. Fritz Lipmann.

Although the money is in hand to build the Research Building, that for equipping it remains to be raised. And this will be very costly, because

as man gets closer and closer to the facts of life of the cell the more intricate, prodigious and expensive become the implements that he needs to extend the range of his knowledge. No longer can the investigator conduct his studies solely with test tube and old-fashioned microscope. He now needs such items as electron microscopes, ultracentrifuges, electrophoretic apparatus and innumerable radiation detectors. All these and more will constitute the scientific furniture of the Massachusetts General Hospital's new research building. To attempt to set up a research institute without such equipment would be equivalent to sending an army against the enemy equipped only with rifles and hand grenades.

The material of the biologic or medical investigator is living tissue — that of man or of animals, for with no other medium can the way to prevent or cure disease be found. The use of such material, however, imposes great responsibility. In experiments on animals, suffering must be minimized. Studies on man must be planned only with the subject's full understanding and consent, and with every protection against all possible injury.

The top floor of the new research building will be a farm for the animals used in research. An animal lover on the Board of Trustees of the hospital, together with the architect and the staff members, has planned this farm to give its inmates conditions optimal for their welfare.

The participation of human patients in research dates from time immemorial. At the Massachusetts General Hospital it has been greatly facilitated by the installation in 1925 of a special ten-bed research ward. This ward already has had a distinguished career, and it is hoped that one day its history will be written down. Already its contributors have enriched the medical literature. Last March it was finally named the Mallinckrodt Ward 4 in honor of Mr. Edward Mallinckrodt, Jr., one of its principal benefactors. The only fault of the research ward is that it is nowhere near large enough. With the opening of the Research Building certain space now occupied by laboratories will be vacated and can be used to double the size of the Mallinckrodt Ward, which is in close prox-

imity to the site of the new building. This juxtaposition is bound to be fruitful.

Already \$1,750,000 has been raised toward the goal of \$2,750,000 announced last year—almost enough to construct the building without equipment. The current drive terminating on January 1, 1950, is confidently expected to bring the fund to practical completion.

ARTHRITIS AND RHEUMATISM FOUNDATION

CHRONIC arthritis, it is said, has stiffened man's backbone for a period estimated at forty-one thousand nine hundred and forty-nine years. His backbone has now been stiffened, it appears, to the point where he is ready to make some unusual efforts in its behalf.

Little enough has been done for arthritis in these days of multi-million-dollar projects, according to available figures. In spite of the fact that about 7,000,000 Americans suffer from some form of arthritis or rheumatic disease, or about one out of every twenty citizens, only \$200,000 a year is being spent on research into the disease and the care of the patients being studied. In contrast to this figure it is interesting to note that \$10,587,000 is currently being expended in the field of cancer research, that during the past year \$18,665,523 was raised in the annual campaign against tuberculosis and \$18,669,299 in that against poliomyelitis and that \$11,000,000 has been appropriated by Congress for the construction of forest trails (but not for the use of arthritic patients).

The Arthritis and Rheumatism Foundation, determined that at last a united effort shall be made to obtain funds with which to fight the Number 1 crippler of mankind, is now engaged in a nationwide campaign. Started before Thanksgiving it will run until nearly Christmas, with General Lucius D. Clay as chairman. The New England Chapter is doing its share and is in addition making a survey of the arthritis clinics in the State with the assistance of the Department of Public Health, and the approval of the Council of the Massachusetts Medical Society, which has also established a subcommittee on arthritis of the Committee on Public Health.

NEW ENGLAND COUNCIL

NEW England medicine had its day—three of them—at the Copley Plaza Hotel in Boston on the occasion of the previously announced eighth annual postgraduate assembly, on November 9, 10 and 11, 1949. The guest speakers on the excellent program were drawn from such diverse points as New York and Baltimore, Chicago, Philadelphia, Durham, North Carolina, Rochester, Minnesota, and Saskatoon, Saskatchewan. The audience, on the other hand, overwhelmingly New Englanders, made up in numbers what they lacked in geographic distribution. 975 physicians registered for the course.

On the premise that postgraduate education is a major factor in medical organization the New England Assembly rates a high mark in the fulfillment of this function.

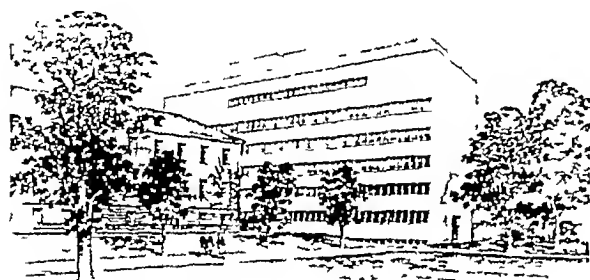
The status of the Council of the New England State Medical Societies and the relations that exist between it and the New England Postgraduate Assembly are confused in the minds of many physicians in the area. They are, in fact, mutual enterprises serving the same general ends, but independent in organization. The Council promotes improvement in medical practice throughout New England, the Assembly, organized and conducted for reasons of convenience by a committee of the Massachusetts Medical Society, is a mutual undertaking of the six New England state societies and enjoys the blessing of their Council.

The Council, composed of three representatives from each state society, met during the course of the Assembly and heard reports on hospital care for the chronically ill by Dr. W. A. R. Chapin, of Springfield, on the unsuccessful attempts at establishing working relations between the Massachusetts Medical Society and the Massachusetts Hospital Association by Dr. A. E. Parkhurst, and on the conference on public relations held in Chicago in November by Dr. John R. Conlin. A dinner for the entertainment and enlightenment of the New England senators and representatives in Congress was discussed and planned for December 18, prior to their return to Washington.

If any valid criticism of the New England Council of State Medical Societies exists, it is that its

old domestic building, where converted kitchens and dining rooms lent themselves well, although far from perfectly, to research purposes. Ultimately most of this building will be devoted to laboratories. The most recent acquisitions of research laboratory space are for the Pediatric and Gynecological services in the Burnham-Vincent Building, which was opened in 1947, and for the Dermatological Service in what was once Ward E and the old Bradlee operating theater.

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in the night was disregarded by her physician. One week before admission, headaches without localization developed, followed by slow speech and increasing drowsiness. Consultants considered encephalitis or some form of poisoning. Death occurred about forty-eight hours after admission to the hospital. There was a cystic glioblastoma multiforme, 4.5 cm in diameter, in the right frontal lobe. The vague initial symptoms were due to the neoplasm itself, and the terminal episode to the sudden enlargement of the cyst.

It should be emphasized that events such as those in these cases can occur in tumors other than glioblastoma multiforme but are more frequent when that tumor is present. Enlargement of a cystic tumor or progressive growth of a tumor in the region of the aqueduct of Sylvius can lead to relatively sudden death as the result of acute hydrocephalus.

Slowly growing neoplasms occasionally cause unexpected death when they involve areas of the brain from which few or no localizing signs are produced. Atrophy and condensation of the brain compensate for their presence until the size of the tumor precludes further adjustment. Death may then be sudden, usually the result of pontine hemorrhage, as in the case of a sixty-nine-year-old man who died three days after a fall, in which he had injured his neck and lost consciousness. He was thought to have sustained a cerebral laceration or a fracture of the spine. Autopsy showed a very large parasagittal meningioma and pontine hemorrhage. Further study of the history uncovered several episodes suggestive of a minor cerebrovascular accident over the few months preceding death.

Small hemorrhages scattered through the pons often result when the vessels of that region become excessively distorted as a consequence of an expanding lesion within the skull. They are the most frequent cause of death in neglected subdural hematoma and, far more often than is usually supposed, in intracranial tumors, regardless of location.

Intracranial tumors are often discovered in medicolegal autopsies when they are the precipitating cause of accidents, as in the case just described. Falls, automobile accidents and other forms of trauma occur as the result of the unsteadiness and mild mental confusion that often precede definite clinical symptoms of intracranial tumor. The primary purpose of this note, however, is to call attention to mechanisms by which unexpected deaths are *directly* produced by the tumors.

ORVILLE T. BAILEY, M.D.

Assistant Professor of Pathology, Harvard Medical School

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CANCER FACT BOOK

The Department has just prepared a new edition of the *Cancer Fact Book*, which contains a series of charts and tables for the use of physicians desiring data on cancer. Copies of this booklet may be obtained on request.

The booklet contains information regarding the services of the State and State-aided cancer clinics and the Tumor Diagnosis Service, as well as the epidemiology of cancer.

At the present time there are six times as many cancer deaths among males and three times as many among females as there were at the beginning of the century.

Adjustments to take into account changes in the age distribution of the population showed that the rates for females have been declining for the past fifteen years. This downward trend has been more marked for Massachusetts than for the country as a whole.

The sites of cancer showing a downward trend are the mouth, skin, stomach and uterus.

About 30 per cent of all deaths, among women between the ages of forty and sixty, are from cancer.

About 13 per cent of all new cancer cases in Massachusetts are seen in the cancer clinics.

About 85 per cent of all patients seen at the cancer clinics are sent by physicians.

The median age of cancer patients seen at the clinics is several years older at present than in 1930.

There is a four-month delay between first recognizable symptoms and first visit to physician, and a two-month additional delay before the first visit to a clinic.

Of the cases of cancer in which the patients attended the cancer clinics, 36 per cent were classified as probably curable, 31 per cent as possibly curable, and 33 per cent as incurable.

Of patients with skin cases seen within the first month, 80 per cent were alive ten years after treatment. Of those seen later than one month about 44 per cent were alive ten years after treatment.

Of patients with cancers other than of the skin, seen within one month, 39 per cent were alive ten years after treatment, and of those seen after one month, 20 per cent were alive ten years after treatment.

Although pain usually has not been considered a symptom of early cancer, it was present in an eighth of all cancer patients who came to the clinics within two months after the first symptom was noticed.

light is still too far under the bushel. Active and interested members of the various New England societies are still unaware of its accomplishments, its aims or even its very existence. There is scarcely a New Englander that is not proud of the traditions, the independent sturdiness and the solidarity of his section of the country. So far as medical standards are concerned, the Council is in a position to aid in preserving all of these, but its activity should be better publicized.

It is announced in the papers that Dr Richardson, of Boston, expelled a tape worm from a patient which was 100 feet long!

Boston M & S J, December 12, 1849

MASSACHUSETTS MEDICAL SOCIETY



TWO-WAY MOBILE RADIOS AVAILABLE

The Federal Communications Commission gives preference to physicians for the use of two-way mobile radios.

The installation cost is \$17.75 per month. The charge for completed calls in both directions is \$0.35, the charge for check-in and check-out is \$0.05 and the charge for location reports is \$0.05. Physicians within a 30-mile radius of the State House who desire to have one of the 300 available units in their automobiles, should communicate at once with American Communications Co., Inc., 272 Centre Street, Newton (Tel DEcatur 2-3630).

H. QUIMBY GALLUPE, Secretary

NOTES FROM THE MEDICAL EXAMINER

UNEXPECTED DEATH DUE TO INTRACRANIAL TUMORS

The symptoms caused by intracranial tumors extend over months or years in the great majority of cases. For this reason, brain tumors would not be expected to appear in the records of the medical examiner except as incidental findings in patients dying of other causes. A survey of records, however, shows that intracranial tumors are found in a considerable number of cases as the principal cause of death. This note is concerned with some of the mechanisms by which unexpected deaths may be brought about by these lesions.

Gliomas that infiltrate and replace cerebral tissue in "silent" areas of the brain, such as the frontal lobes and portions of the occipital lobes, may attain large size without producing symptoms sufficiently clear-cut to justify careful clinical study. Another such region is the corpus callosum. All too often, the early signs are psychic in nature and are regarded as manifestations of mental instability. The number of unexpected intracranial tumors found at autopsy in mental institutions shows that recognizable manifestations may be wholly of this character throughout the course of a long illness. Meningeal tumors pressing on "silent" areas may enlarge slowly over many years without producing clinical symptoms because compensatory mechanisms allow for the increase in intracranial volume.

The point at which distinctive clinical symptoms are produced is the onset of increased intracranial pressure. This is due either to a sudden increase in intracranial volume, which does not allow time for the compensatory mechanisms to come into play, or to a gradual enlargement, which finally taxes these mechanisms beyond their limits, at which point death may ensue very quickly.

The abrupt and unexpected increase in volume of intracranial contents resulting from a tumor is usually due to a large hemorrhage, especially in a glioblastoma multiforme. The blood vessels in this glioma characteristically show atypical proliferation, which predisposes them to rupture. Glioblastoma multiforme has a tendency to replace considerable amounts of brain tissue, thus delaying the onset of increased intracranial pressure until the tumor is large.

A typical case was that of an eighteen-year-old college student who complained of lack of ability to concentrate, blurred vision and headache of three weeks' duration, thought to have been caused by the strain of examinations. After the examinations, he was admitted to the hospital for study. For fifteen days, he was asymptomatic except for mild headaches. On the sixteenth day, the headaches suddenly became very severe, and a tonic convulsion occurred, followed by shock, respiratory failure and death. At autopsy, a huge glioblastoma multiforme was found in the corpus callosum extending into both occipital lobes. There was massive intraventricular and subarachnoid hemorrhage from blood vessels of the tumor.

Many gliomas become cystic. Although neoplastic cysts usually enlarge slowly, they may expand much more rapidly, causing the symptoms to be sufficiently bizarre to make clinical diagnosis difficult and leading to the suspicion of poisoning or trauma to the head.

In such a case a sixty-five-year-old woman was admitted to the hospital because of stupor for twenty-four hours. The statement of a relative that the patient had for some weeks made repetitious comments and had wandered about the house

spring of nondiabetic parents, or to the therapeutic omission of the use of glucose in perhaps the largest series of infants born of diabetic mothers reported from one clinic.

A doctor or student who wishes to investigate a problem in diabetes will find the book full of suggestions.

The book is heartily recommended—minus the diet tables, which could be summarized and thus reduce the cost and make it available to more readers. Moreover, the diet of any diabetic patient varies from day to day according to exercise and mode of life, and he must be taught how to make adjustments.

Practical Aspects of Thyroid Disease By George Crile, Jr., M.D. 12°, cloth, 355 pp., with 101 illustrations. Philadelphia: W. B. Saunders Company, 1949. \$6.00.

This monograph of 355 pages presents in a large measure the personal experience of the author in diagnosis and treatment of diseases of the thyroid gland. In an effort to make the volume succinct and perhaps more practical, the author purposely avoids presenting a study of the much larger accumulated material of thyroid pathology from the Cleveland Clinic gathered under George Crile, Sr., and his associates. In only a few less common pathologic conditions of the thyroid gland does he employ this fuller material in his discussion, this too, however, is interpreted very much in the light of his own personal experience.

The book opens with a brief discussion of the physiology and pathology of the thyroid gland and presents well established concepts generally accepted in the prevention and treatment of endemic goiter. The material is divided into chapters dealing with the diagnosis and the treatment of hyperthyroidism in its various aspects and dealing also with the various complications of treatment of thyroid disease. Antithyroid therapy both as primary medical treatment and as a preparation for surgery is discussed, and a very brief discourse is given on radioactive iodine. The reviewer does not entirely agree with the author that radioactive iodine is "safe, effective and simple," and believes such conclusions are not yet warranted in the light of insufficient experience to substantiate such a statement. The author does, however, advise caution in the employment of this drug but concludes that radioactive iodine bids fair to become the preferred treatment for all patients with Graves' disease. This the reviewer very much doubts and would caution that this material be used only in the hands of those thoroughly trained in the use of irradiated isotopes.

The description of the technic of thyroidectomy is outlined as practiced by the author. In all probability this is not the technic that has been employed in the past in the Cleveland Clinic. The surgical technic as described, however, is sound and practical and, in general, similar to that advocated in other large thyroid clinics in the country. One is glad to note that exposure of the recurrent laryngeal nerves is advocated. The volume proceeds, then, with a discussion of the various pathologic conditions of the thyroid gland such as thyroiditis and carcinoma. A brief chapter is given, also, on the types of anesthesia. It is interesting to note that the old arguments for the use of local anesthesia are still in force, and the dictum is advanced that a more adequate respiratory exchange can be obtained with greater ease under local anesthesia than in patients who are relaxed under general anesthesia. Certainly, this would not be agreed to by everyone, respiratory exchange can be obtained in all types of thyroid conditions under general anesthesia if an endotracheal catheter is used. In the hands of expert anesthesiologists, intratracheal anesthesia can be employed without trauma and without any increased morbidity and certainly adds to the patient's comfort and greatly reduces the possibility of obstruction.

The chapter on carcinoma of the thyroid gland reflects almost entirely the views of the Cleveland Clinic and in a large measure represents the work of Dr. Allen Graham. The descriptions of the various types of carcinoma arising in the gland are in large measure similar to other classifications but perhaps are not quite so practical as the classification given by Warren and Meissner. One also is at a loss to understand whether the author advocates the removal of discrete adenomas, which in so many clinics are thought to be very definite precursors of carcinoma of the thyroid gland or whether he prefers to wait until the clinical diagnosis of carcinoma is made before discrete adenomas are removed.

This discussion does not present a completely convincing argument for or against such now quite universally accepted prophylaxis.

The material is well presented, well organized and extremely well illustrated. It should prove valuable to the general practitioner who does not have a large experience in the treatment of thyroid disease, but it would not be of great help to the internist or surgeon who has had a reasonably large experience in the recognition and treatment of various pathologic conditions of the thyroid gland.

A moderate number of cross references is given. To the critical reader, if he desires, they present sufficient material to clear up certain controversial points that are not entirely clarified in this volume.

The book is well printed and it is to be recommended to the type of reader mentioned above.

Food and Facts for the Diabetic By Joseph H. Barach, 8°, cloth, 113 pp., with 16 illustrations and 21 tables. New York: Oxford University Press, 1949. \$4.00.

This volume consists of 113 pages of text, including tables and index, but also 198 unnumbered pages on which are 232 diets for men and women of the ages of twenty-five and above, as well as diets for children and emergencies. The diets are calculated on the basis of body build—small, medium and large—for 250, 275 and 300 calories per kilogram of body weight respectively. One could hardly blame the patient if he asked why he should purchase so many diets that are not designed for him.

The text is admirable, and one would hope that all diabetic patients would become familiar with it, although the style is rather more for nurses and dietitians and the more intelligent diabetic patients than for the rank and file. The advice given the patients is stated so clearly and is so sound that it would be meticulous and, indeed, unfair to point out the few sentences or even paragraphs, which undoubtedly will be altered in a subsequent edition.

NOTICES

MISSISSIPPI VALLEY MEDICAL SOCIETY

The fifteenth annual meeting of the Mississippi Valley Medical Society will be held at Springfield, Illinois, on September 27, 28 and 29, 1950, under the presidency of Dr. N. G. Alcock, of the University of Iowa.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1950 ESSAY CONTEST

The Tenth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1950. The Society will offer a cash prize of \$100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Fifteenth Annual Meeting of the Mississippi Valley Medical Society to be held in Springfield, Illinois, September 27, 28 and 29, 1950, the Society reserving the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1950. The winning essays in the 1949 contest will appear in the January, 1950, issue of the *Mississippi Valley Medical Journal*.

Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

POSITION FOR QUALIFIED BACTERIOLOGIST IN VETERANS ADMINISTRATION

A vacancy exists for a qualified bacteriologist in the pathology laboratory of the Veterans Administration Center, Los Angeles 25, California. The laboratory is located in the

CORRESPONDENCE

ON THE SOUNDS OF THE HEART

To the Editor I have admired the painstaking and scholarly quality of Dr. Orias's article on heart sounds in the issue of November 17, of the *Journal*. But is this not an instance of how the attempt to apply graphic instrumental methods has made obscure a matter which is readily clarified by simple observation?

To summarize what I wrote many years ago in the *New England Journal of Medicine*, in an article entitled "The Cause of the First Heart Sound" (200 917, 1929), the first heart sound is a tone produced by the sudden assumption of tension by the structures surrounding the ventricular cavities — namely, the ventricular walls and the mitral and tricuspid valves — as the diastolic collapse of the ventricular walls is converted suddenly to a state of tense convexity by systole.

Simple illustrations of comparable tones are as follows. If one pulls sharply on the edge of a handkerchief, previously in loose folds, a tone is produced. If the sail of a boat is suddenly filled by a gust of wind a tone is produced. Or if one blows sharply into a collapsed paper bag a tone is produced. The similar nature of the first heart sound is unmistakable if one observes the exposed heart of a large dog.

If one looks closely at the freely exposed heart of such an anesthetized dog, one sees that there is, in diastole, an instant of flaccid concavity of the anterior surface (the right ventricle) that flaps suddenly into a hard convexity as systole becomes effectual. And if one listens with a small, lightly applied stethoscope the conclusion is inescapable that it is this sudden resumption of convexity and tension that produces the first sound.

Undoubtedly, if one skilled in delicate physiologic technique were to take multiple lymographic tracings of the ventricular surface and of intraventricular pressure, all synchronized with a phonocardiogram, one would obtain objective confirmation of this. But where the mechanism is so clear to anyone who will look, feel and listen understandingly it seems unnecessary to go farther.

FRANCIS W. PALFREY, M.D.

Boston, Massachusetts

TREATMENT OF THROMBOEMBOLIC DISEASE

To the Editor I was very much interested in the recent article on pulmonary embolism by Roe and Goldthwait in the November 3 issue of the *Journal* and also in the editorial on the same subject appearing in that issue.

I realize full well the importance of statistical analyses, and I also am well acquainted with the fallacy of relying upon them to chart one's course in therapeutics, especially if the statistics do not take into consideration all the pertinent data. It is unfortunate that the authors did not correlate their autopsy statistics with general hospital population according to age and disease and also the magnitude of the operative procedures in the different periods in an effort to determine the true cause of the increased incidence of fatal embolism rather than to blame it on the failure of femoral-vein interruption, as a method of treating thromboembolic disease.

Realizing what an important step in the treatment of thromboembolic disease that interruption of femoral veins has been since Homans first described it in 1934 and for fear that this article will be quoted (as it already has to me as damning evidence that the procedure is of little value in the therapy of this disease), I feel it my duty to point out that the increased number of cases of fatal embolism at the autopsy table in the past five-year period, 1943-1947, certainly is not because this method has failed in the majority of patients that have been so treated. In fact, the inference that should be drawn from the statistics quoted in the article is that more patients should have had their femoral veins interrupted, since in this five-year period interruption was performed in only 10 of the 92 fatal pulmonary emboli. It should also be pointed out that this method of treating thromboembolic disease was not generally accepted throughout the Massachusetts General Hospital. In fact, it was only on the East Surgical Service while Dr. Arthur W. Allen was chief and on his patients and mine and a few others on the private side that a policy was carried out in which femoral-vein interruption was the method

of choice in the treatment of thromboembolic disease in all its various manifestations.

There is no question that this article is an important one, since it draws to the reader's attention that we have not solved the problem of thromboembolic disease. The subject certainly needs further investigation, but until we have better methods at our disposal to prevent massive pulmonary embolism the operation of femoral-vein interruption in the hands of a competent surgeon should not be discarded. Those that recommend it fully realize that it is not a perfect procedure, but let us not incriminate it too severely from this report, when in 92 cases of fatal pulmonary embolism it was not used in 82, or 89 per cent.

ROBERT R. LINTON, M.D.

Brookline, Massachusetts

BOOK REVIEWS

Diabetes and its Treatment By Joseph H. Barach, M.D. 8¹/₂ cloth, 326 pp., with 73 illustrations, 50 tables, and 2 plates. New York: Oxford University Press, 1949. \$10.00.

This book is written by an author who knows diabetes well and deserves the approbation of every physician in the United States for his courage in exposing diabetic quackery wherever found. Unfortunately, the book is expensive, because it contains 326 numbered pages and approximately 200 unnumbered pages devoted to a system of diets for men, women and children, all of which are duplicated in his other book, entitled *Food and Facts for the Diabetic*, which was written for patients. There are 73 figures and 60 tables.

Commendable initiative throughout is shown by the writer. He draws upon his own practice to illustrate the advantages of this or that kind of treatment. The volume is decidedly *suus generis*, although the literature is also very well covered. The text is expressed forcibly, and nearly every page is thought provoking, for example, "Obviously the diabetes that appears at the age of 10 will have many more years to produce changes in the tissues and organs of the body than the diabetes that comes at 60, so that the later in life that diabetes appears, the less chance it has to shorten life." One wonders whether the diabetes that is diagnosed at the age of sixty has not been latent in many cases for a decade or more and, therefore, whether the foregoing really states the situation fairly. Best and Kendall Emerson, Jr., have both intimated the presence of a prediabetic diabetic era and the need for the vigorous and active treatment of such cases. At present this can be done only by the prophylaxis of obesity. The following statement about obesity is worth wide dissemination: "Since there is no known advantage in being overweight, we may very well offer the blanket advice to everyone to avoid obesity." Dr. Barach is equally incisive about the marriage of a diabetic person: "My advice to a young member of my own family would be not to marry a diabetic, and my advice to a diabetic would be not to marry at all, unless other conditions in his or her life are favorable." In dealing with heredity, however, the author inadvertently has given a wrong impression in stating that all the children of two diabetic parents will develop diabetes. Theoretically, they will develop diabetes, but practically they will not do so unless they live long enough to reach the age at which diabetes is likely to break out. The chances have been computed that before those ages are reached at least half the offspring will die of other diseases.

Throughout the volume one finds words of wisdom and new viewpoints when old problems are presented. There is an instructive table of the common complaints of the patient and a novel discussion of weights and diets. Deformities are recognized as occurring quite often in the children of diabetic parents, and the author also calls attention to the frequency with which lesions of the feet of older patients are connected with and often dependent upon congenital deformities of the feet themselves. It is unfortunate that when the 47 per cent mortality and even 45 per cent mortality for thigh operations upon diabetic patients in certain localities are referred to, attention is not called to the low mortality of McKinnick and his group — 5.5 per cent, according to a recent paper in the *Annals of Surgery* (130:826, 1949) — and to their conclusions that transmetatarsal operations make many thigh operations unnecessary. Reference is made to the routine practice of giving glucose to the children just born of diabetic mothers, but attention is not called to the hypoglycemia, which is often found in the off-

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GENERALIZED INTESTINAL POLYPOSIS AND MELANIN SPOTS OF THE ORAL MUCOSA, LIPS AND DIGITS*

A Syndrome of Diagnostic Significance

HAROLD JEGHERS, M D,† VICTOR A. McKUSICK, M D,‡ AND KERMIT H. KATZ, M D§

WASHINGTON, D C, BALTIMORE, MARYLAND, AND BOSTON, MASSACHUSETTS

IN 1944, a brief report was made by one of us¹ regarding the association, in 2 patients, of a distinctive type of melanin pigmentation of the oral mucosa, lips and digits with intestinal polyposis.

Since then 10 cases, including the 2 referred to above, have been collected from five different hospitals and are reported here in detail along with a review of pertinent literature and a discussion of the significance of this syndrome.

CASE REPORTS

CASE 1 A 14-year-old American schoolgirl entered the Fifth Medical Service of the Boston City Hospital on March 11, 1939, with the complaint of persistent diarrhea of 6 weeks' duration. There were five or six watery bowel movements each day. No mucus, blood or fat was ever noted in the stools. Intermittently during this period there were bouts of vomiting. Her appetite was good. There was no pain, but the patient noted frequent loud gurgling noises in the abdomen. During the present illness there was a 4-pound weight loss.

Twice in 1935 she had been operated upon at another hospital for intussusception and intestinal obstruction. On the second occasion a portion of the ileum was resected. Polyps of the stomach, ileum and sigmoid were found at that time. So far as could be ascertained the family history was non-contributory. The parents believed the spots on the lips had been present since early childhood and apparently had not changed over the years.

Physical examination revealed a thin, rather undernourished patient appearing acutely ill. The hair and irides were dark brown. The skin was pale. On the face, concentrated about the mouth, and on the lips and oral mucous membrane were numerous small, brown-black spots. Similar areas of pigmentation were noted on the dorsal surface of the fingers (Fig. 1). A few pigmented spots were also observed on the toes. There were two small patches of vitiligo on the back. The heart and lungs were normal. The abdomen was moderately distended, with tenderness over the upper half. Loud borborygmi were present. The liver edge was palpable two fingerbreadths below the right costal

margin. There was slight clubbing of the fingers and toes. Examination otherwise was negative.

The blood pressure was 85/40.

Examination of the blood showed a red-cell count of 2,410,000, with a hemoglobin of 70 per cent, and a white-cell count of 7400, with a normal differential count. The red cells were slightly hyperchromic and macrocytic. The blood Hinton test was negative. The urine was normal. The stools were loose, brown and guaiac negative. Gastric analysis revealed 24 units of free hydrochloric acid and 46 units of total acid. Barium-enema study by the double contrast method showed multiple negative shadows consistent with polyps scattered throughout the large intestine. Many small clusters of two to four polyps in the sigmoid and rectum were directly visualized on sigmoidoscopic examination. No areas of pigmentation were noted.

A regimen of symptomatic measures supplemented by frequent administration of liver extract and iron resulted in disappearance of the diarrhea, with improvement in weight and a subjective feeling of well-being, and with an increase in the hemoglobin to 88 per cent and in red-cell count to 3,300,000. The patient was discharged after 6 weeks in the hospital.

On August 19, she was readmitted to the hospital because of a return of diarrhea during the preceding month. The findings were as on the previous entry, and satisfactory improvement resulted from similar therapy. She was discharged in 3 weeks.

Lobar pneumonia due to a Type I pneumococcus necessitated readmission on November 21. There was no bacteremia. Treated with sulfapyridine and general supportive measures, she failed to show any response and died on December 1.

At autopsy pigmentation of the skin as previously described was noted.

Death was due to lobar pneumonia of the right lung. The pleural cavity was normal, as were the heart and pericardial cavity.

The esophagus was normal. The mucosa of the stomach bore three soft pedunculated polyps ranging from 1.5 to 2.5 cm in diameter, one lying just below the cardiac orifice, a second on the greater curvature, and a third near the pyloric sphincter of the stomach. The mucosa otherwise was normal, as was the duodenum. The jejunum and ileum showed some brownish-black, granular pigment along the edge of the mucosal folds. In addition, a polyp occurred every 50 to 60 cm. These averaged 1 to 2 cm in diameter and were attached to pedicles that were 0.5 to 1.0 cm in length. The terminal ileum contained the largest polyp in the gastrointestinal tract, this measured 4.5 cm in diameter. One mulberry-like polyp measuring 1.5 cm was present in the sigmoid portion of the large intestine.

The liver weighed 1960 gm. It was of normal color and consistence and on section bore the usual geographic markings. Microscopical examination showed lipid vacuolization of the liver cells at the central portions of the lobules.

*From the Fifth and Sixth (Boston University) Medical Services, Boston City Hospital, and the Department of Medicine, Boston University School of Medicine; the Medical Clinic and School of Medicine, Johns Hopkins University and Hospital, and the Department of Medicine, Georgetown University School of Medicine.

†Director and professor, Department of Medicine, Georgetown University School of Medicine; physician-in-chief, Georgetown University Hospital; consulting physician, Boston City Hospital.

‡Assistant in medicine, Johns Hopkins University School of Medicine.
§Assistant director, Fifth and Sixth (Boston University) Medical Services, Boston City Hospital; assistant professor of medicine, Boston University School of Medicine.

General Medical and Surgical Hospital of the Center. The position pays \$6400 a year, and the Civil Service classification is known as GS-12.

Applicants must have successfully completed a full four-year course leading to a degree with major study in the biologic sciences in a college or university of recognized standing, with courses totaling at least twenty semester hours in general and medical bacteriology, or any combination of bacteriology and biology including at least ten semester hours in general and medical bacteriology. Applicants must show four years' experience, at least two years of which includes experience in medical bacteriology in a research or clinical laboratory. The other years may include experience in teaching medical bacteriology in a medical school of recognized standing. A doctor's degree in bacteriology or serology may be substituted for the latter experience.

Interested applicants are urged to send Standard Form 57 (blanks can be obtained at any post office) to the Personnel Officer, Veterans Administration Center, Los Angeles 25, California.

FUNDS FOR RESEARCH IN CARDIOVASCULAR DISEASE

A portion of the funds collected during the 1949 Heart Campaign has been set aside for research in cardiovascular diseases, according to C. Sidney Burwell, M.D., chairman of the Research Allocations Committee of the Greater Boston Chapter of the Massachusetts Heart Association.

Applications from institutions in Greater Boston are invited. Inquiries should be addressed to Dr. Burwell at the Peter Bent Brigham Hospital, Boston.

DAMON RUNYON CLINICAL RESEARCH FELLOWSHIPS

The American Cancer Society announces the availability of Damon Runyon Clinical Research Fellowships. These fellowships, inaugurated last year, are made possible by a grant from the Damon Runyon Memorial Fund for Cancer Research to the American Cancer Society. They are administered by the Society upon recommendation of the Committee on Growth of the National Research Council. In most cases a fellowship will provide a period of training in a hospital under the guidance of a qualified clinical investigator. However, fellowships may be awarded for training in a basic science provided that such training is directed toward preparing the fellow for clinical cancer research. They are limited to men and women holding the M.D. degree. It is emphasized that they are intended to promote training in clinical cancer research rather than in cancer diagnosis and therapy.

Applications submitted prior to March 1, 1950, will be acted upon during April. Fellowships approved at that time may become effective July 1, 1950, or at such other time as will meet the convenience of the fellow and the institution. Communications should be addressed to the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D.C.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3-MAY 19 Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286. Issue of August 18.

DECEMBER 17 Guest Speakers' Conference. Bone Marrow Aspiration in Diagnosis of Disorders of the Blood. Dr. Simon Propp. Staff Conference. Room The Springfield Hospital Springfield. 11:00 a.m.

DECEMBER 19 Boston Lying in Hospital Obstetric Round Table. Page 888. Issue of December 1.

DECEMBER 20 South End Medical Club. Page 888. Issue of December 1.

DECEMBER 20 Boston City Hospital House Officers' Association. Page 950. Issue of December 8.

DECEMBER 21 Association of School Physicians of Massachusetts. Page 950. Issue of December 8.

DECEMBER 28 AND 29 American Association for the Advancement of Science. Page 350. Issue of September 1.

JANUARY 9 New England Cardiovascular Society. Page 724. Issue of November 3.

JANUARY 9-DECEMBER 1 Laboratory Courses at Communicable Disease Center Atlanta Georgia. Page 950. Issue of December 8.

JANUARY 12 Common Skin Diseases. Dr. John L. Fromer. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JANUARY 18-20 Conference on Cardiovascular Diseases. Page xvii. Issue of November 10.

FEBRUARY 20 Boston Lying in Hospital Obstetric Round Table. Page 888. Issue of December 1.

FEBRUARY 20-23 American Academy of General Practice. Page 254. Issue of August 11.

APRIL 17 Boston Lying in Hospital Obstetric Round Table. Page 888. Issue of December 1.

APRIL 24-28 National Tuberculosis Association. Page 678. Issue of October 27.

MAY 3 Norfolk District Medical Society Anniversary Dinner.

MAY 16-18 Massachusetts Medical Society Annual Meeting. Hotel Statler Boston.

JULY 17-22 International Congress for Scientific Research. Page xvii. Issue of September 1.

AUGUST 21-26 International Society of Hematology. Page 888. Issue of December 1.

SEPTEMBER 27-29 Mississippi Valley Medical Society. Page 991.

DISTRICT MEDICAL SOCIETY

NORFOLK

JANUARY 24

FEBRUARY 28

MARCH 28

MAY 3 Anniversary Dinner

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 22

FRIDAY DECEMBER 23

*9:00 a.m.-12:00 p.m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*1:30 p.m. Tumor Clinic. Out Patient Department. Mount Auburn Hospital, Cambridge.

TUESDAY DECEMBER 27

*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

WEDNESDAY, DECEMBER 28

*12:00 p.m. Clinical Conference. Margaret Jewett Hall. Mount Auburn Hospital, Cambridge.

*Open to the medical profession.



*Dr. Wise, as a holiday measure
That his neighbors and relatives treasure,
Puts his Journal away
For some part of the day
And devotes himself wholly to pleasure*

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GENERALIZED INTESTINAL POLYPOSIS AND MELANIN SPOTS OF THE ORAL MUCOSA, LIPS AND DIGITS*

A Syndrome of Diagnostic Significance

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IN 1944, a brief report was made by one of us¹ regarding the association, in 2 patients, of a distinctive type of melanin pigmentation of the oral mucosa, lips and digits with intestinal polyposis.

Since then 10 cases, including the 2 referred to above, have been collected from five different hospitals and are reported here in detail along with a review of pertinent literature and a discussion of the significance of this syndrome.

CASE REPORTS

CASE 1. A 14-year-old American schoolgirl entered the Fifth Medical Service of the Boston City Hospital on March 11, 1939, with the complaint of persistent diarrhea of 6 weeks' duration. There were five or six watery bowel movements each day. No mucus, blood or fat was ever noted in the stools. Intermittently during this period there were bouts of vomiting. Her appetite was good. There was no pain, but the patient noted frequent loud gurgling noises in the abdomen. During the present illness there was a 4-pound weight loss.

Twice in 1933 she had been operated upon at another hospital for intussusception and intestinal obstruction. On the second occasion a portion of the ileum was resected. Polyps of the stomach, ileum and sigmoid were found at that time. So far as could be ascertained the family history was non-contributory. The parents believed the spots on the lips had been present since early childhood and apparently had not changed over the years.

Physical examination revealed a thin, rather undernourished patient appearing acutely ill. The hair and irides were dark brown. The skin was pale. On the face, concentrated about the mouth, and on the lips and oral mucous membrane were numerous small, brown-black spots. Similar areas of pigmentation were noted on the dorsal surface of the fingers (Fig. 1). A few pigmented spots were also observed on the toes. There were two small patches of vitiligo on the back. The heart and lungs were normal. The abdomen was moderately distended, with tenderness over the upper half. Loud borborygmi were present. The liver edge was palpable two fingerbreadths below the right costal

marginal. There was slight clubbing of the fingers and toes. Examination otherwise was negative.

The blood pressure was 85/40.

Examination of the blood showed a red-cell count of 2,400,000 with a hemoglobin of 70 per cent, and a white-cell count of 7400, with a normal differential count. The red cells were slightly hyperchromic and macrocytic. The blood Hinton test was negative. The urine was normal. The stools were loose, brown and guaiac negative. Gastric analysis revealed 24 units of free hydrochloric acid and 46 units of total acid. Barium-enema study by the double contrast method showed multiple negative shadows consistent with polyps scattered throughout the large intestine. Many small clusters of two to four polyps in the sigmoid and rectum were directly visualized on sigmoidoscopic examination. No areas of pigmentation were noted.

A regimen of symptomatic measures supplemented by frequent administration of liver extract and iron resulted in disappearance of the diarrhea, with improvement in weight and a subjective feeling of well-being, and with an increase in the hemoglobin to 88 per cent and in red-cell count to 3,300,000. The patient was discharged after 6 weeks in the hospital.

On August 19, she was readmitted to the hospital because of a return of diarrhea during the preceding month. The findings were as on the previous entry, and satisfactory improvement resulted from similar therapy. She was discharged in 3 weeks.

Lobar pneumonia due to a Type I pneumococcus necessitated readmission on November 21. There was no bacteremia. Treated with sulfapyridine and general supportive measures, she failed to show any response and died on December 1.

At autopsy pigmentation of the skin as previously described was noted.

Death was due to lobar pneumonia of the right lung. The pleural cavity was normal, as were the heart and pericardial cavity.

The esophagus was normal. The mucosa of the stomach bore three soft pedunculated polyps ranging from 1.5 to 2.5 cm. in diameter, one lying just below the cardiac orifice, a second on the greater curvature, and a third near the pyloric sphincter of the stomach. The mucosa otherwise was normal, as was the duodenum. The jejunum and ileum showed some brownish-black, granular pigment along the edge of the mucosal folds. In addition, a polyp occurred every 50 to 60 cm. These averaged 1 to 2 cm. in diameter and were attached to pedicles that were 0.5 to 1.0 cm. in length. The terminal ileum contained the largest polyp in the gastrointestinal tract, this measured 4.5 cm. in diameter. One mulberry-like polyp measuring 1.5 cm. was present in the sigmoid portion of the large intestine.

The liver weighed 1960 gm. It was of normal color and consistence and on section bore the usual geographic markings. Microscopical examination showed lipid vacuolization of the liver cells at the central portions of the lobules.

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The spleen weighed 260 gm. Its capsular surface was dark purple and wrinkled. Microscopically the features of congestion were prominent. Both adrenal glands were considerably smaller and thinner than normal, but showed no abnormality on microscopical examination. The uterus appeared smaller than usual, the left ovary contained two small cysts.

The vertebral bone marrow showed granulocytes in all phases of development, numerous stem cells were present



FIGURE 1 Appearance of the Patient in Case 1

Note the spots distributed thickly on and around the lips and sparsely over the bridge of the nose. Highlight in the photograph prevents the clear view of the spots on the fingers of the right hand.

There were moderate numbers of nucleated red blood cells and occasional scattered hemosiderin-filled macrophages.

Microscopical examination of the jejunal mucosa showed the tips of many villi to be club shaped and filled with macrophages containing large clumps of hemosiderin. Well differentiated adenomatous cells comprised the mucosal polyps.

CASE 2. A 39-year-old housewife of Italian-French descent entered the Boston City Hospital on October 22, 1939. For the previous 9 months she had noted increasing constipation requiring frequent enemas. In addition there was intermittent rectal bleeding. Twenty-four hours prior to entry, a mass, which was very painful and bled on attempts at replacement, protruded from the rectum.

Twenty years previously the right fallopian tube and ovary had been removed because of chronic pelvic disease. Five years before the final admission a cholecystectomy was performed after indigestion and pain in the right upper quadrant of the abdomen of 1 year's duration. Three years later the patient was observed in the hospital because of recent onset of anorexia, nausea and vomiting. A gastrointestinal x-ray series revealed irregularity of the stomach and displacement of the duodenal cap, interpreted as being due to postoperative perigastric and periduodenal adhesions.

The patient's parents and husband were living and well. She had had 4 miscarriages. There were 2 healthy children. A first cousin (Case 4) and this cousin's daughter (Case 5) both suffered from complaints referable to the gastrointestinal system. There was no familial tendency to freckles.

Physical examination revealed a well developed and fairly well nourished woman. There were numerous brown and bluish-brown pigmented spots on the face about the eyes

and the mouth, on the lips and gums and on the fingers and toes. These averaged 1 to 3 mm in diameter (Fig. 2). There was no pigmentation elsewhere on the body. The hair was black, and the eyes dark brown. The head was normal. The lungs were clear. The heart was not enlarged, and the rate was 80, with a regular rhythm and sounds of good quality. A soft systolic murmur was audible at the apex. There were no thrills or rubs. The abdomen was soft and not distended, in the lower abdomen there was moderate tenderness, and a poorly defined movable mass was palpated in the right lower quadrant. The rectum was found to be prolapsed and external hemorrhoids were visible. There was slight clubbing of the fingers.

The blood pressure was 108/70.

Examination of the blood showed a red-cell count of 4,160,000, with a hemoglobin of 85 per cent, and a white cell count of 7500, with a normal differential count. The blood Hinton test was negative, as was examination of the urine. The stools were tarry black and gave a +++ guaiac reaction. A gastrointestinal x-ray series revealed multiple polyps of the small and large intestine.

A series of operations was embarked upon: ileostomy, partial colectomy, fulguration of polyps in the rectosigmoid and anastomosis between the ileum and rectosigmoid. In

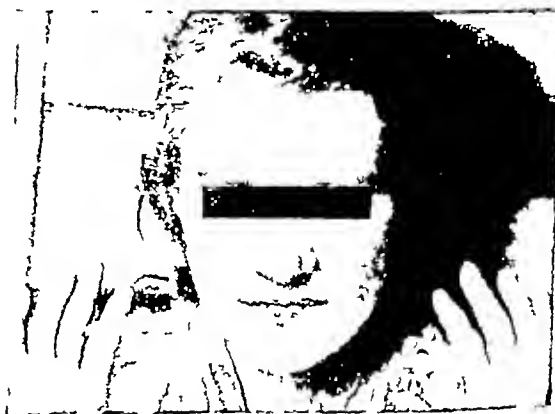


FIGURE 2 Appearance of the Patient in Case 2

Note the density of the spots on the lips. Melanin spots on the fingers are readily noticeable in this photograph.

Initially, the patient showed some improvement, but after the last procedure there was considerable intraperitoneal and wound infection, and evidence of the development of a fecal fistula to the abdominal wall. She began to fail rapidly in weight and strength and died on March 14, 1940.

At autopsy pigmentation of the skin as previously described was noted. Examination of the pericardial cavity was negative. The heart was normal in size and weight. The aortic valve was slightly thickened, the right and posterior cusps were fused along the entire length of the commissure. The tricuspid valve contained only two well formed leaflets and appeared identical with the mitral valve. The foramen ovale and ductus arteriosus were closed.

Examination of the pleural cavity was negative. The lungs were of normal size and weight. The right lung contained an azygos lobe.

The peritoneal surfaces were grayish yellow, with a marked amount of thin, foul-smelling exudate. A pelvic abscess was found at the site of anastomosis of the ileum and rectosigmoid. The superior mesenteric artery originated from the celiac axis. The stomach contained a 1.0-cm sessile polyp in the middle portion of the greater curvature, the mucosa was otherwise normal. In the duodenum the mucosa contained 10 pedunculated polyps varying from 0.8 to 2.0 cm in diameter. The pedicles were from 0.5 to 3.0 cm in length and all were approximately 3 to 5 mm in thickness. There was 1 small polyp of the jejunum, and 8 in the ileum, all being pedunculated and varying in size as those described.

in the duodenum. The entire mucosa of the small intestine was brown gray, giving the appearance of fish skin. The rectum contained several cherry-red fungating polyps, 2 or 3 cm in size. The liver, spleen, kidneys and adrenal glands were normal.

Microscopical examination of the jejunal polyp showed it to be composed of acini of tall columnar cells, some of which were goblet cells, radiating from a fibromuscular pedicle.

CASE 3* A 22-year-old woman was admitted to the Rhode Island Hospital, Providence, Rhode Island, on November 16, 1936, because of periodic abdominal pain of 3 months duration consistent with the diagnosis of intussusception.

The family and past histories were irrelevant. No information about the duration of the oral pigment spots in the patient or their possible presence in her forebears was available.

Physical examination of the mouth and face revealed many small melanin spots on the lips and on the mucosa of the inside of the mouth (Fig. 3). Information regarding spots on the hands and feet was not available.

At operation an intussusception of the terminal ileum due to a polyp was found and a hard mass in the small intestine about 50 cm from the cecum proved to be an adenocarcinoma of the ileum. Resection of this lesion and side-to-side anastomosis were done, with good results and an uneventful



FIGURE 3 Appearance of the Buccal Mucosa in Case 3. Note the size and distribution of melanin spots on the buccal mucosa. Those on the lips are readily seen despite the presence of lipstick. Relatively few are present on the skin about the mouth. (Photograph published through the courtesy of Dr. F. Ronchese of Providence, Rhode Island.)

recovery. Polyps of the stomach were said to have been present also.

The patient was seen periodically for follow-up study. In August, 1937, another operation was performed because intestinal obstruction was suspected. A band of tissue was excised. In January, 1939, she again had an episode suggestive of intestinal obstruction. In July 1940, she was operated upon for recurrent abdominal pain. Large polyps were found in the stomach near the pylorus and in the ileum and appropriate surgical therapy was applied. After this she was symptom-free for 2 months.

In November abdominal pain and obstructive signs recurred. At operation intussusception was seen and polyps of the stomach, jejunum and ileum noted. In March 1942, intussusception due to small-gut polyps again necessi-

tated operation, at this time the additional diagnosis of polyposis of the large intestine was added to the patient's record. At the last report in September 1944, the patient was working regularly and free of complaints.

CASE 4 A 30-year-old housewife of Italian ancestry was admitted to the Boston City Hospital on November 2, 1935. She complained of mid-abdominal pain, intermittent and colicky, of 2 days' duration. Two years previously there had been two similar attacks which had subsided spontaneously. There was a history of chronic constipation. Three years previously an appendectomy had been performed.

The family history was irrelevant except for the occurrence of pigmentation of the face, similar to the patient's in her

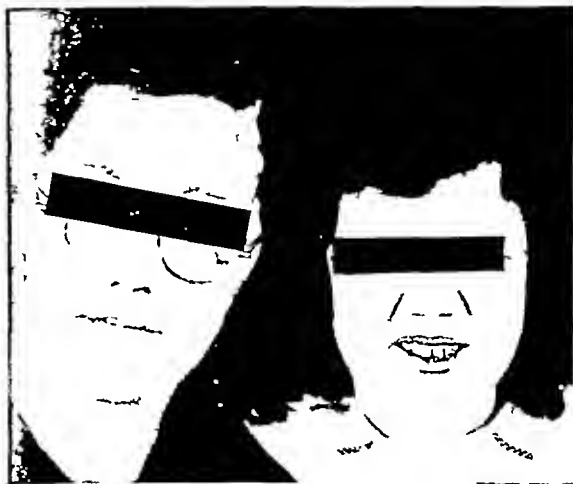


FIGURE 4 Pigmentary Pattern Similar in Mother (Case 4) and Daughter (Case 5).

Note the main distribution in each on and about the lips.

father and her paternal grandmother, as well as in her own daughter (Case 5) and her first cousin (Case 2).

Physical examination revealed a well developed and well nourished woman who appeared acutely ill. The temperature was 99°F. There were numerous small brown-black pigmented areas on the lips, oral mucosa and nose (Fig. 4), and a few on the fingers and toes. The lungs were clear. The heart was normal. The blood pressure was 120/78. Abdominal examination revealed tenderness immediately above and to the left of the umbilicus where a small, firm mass was intermittently palpable. There was no muscle spasm. The white-cell count was 15,000.

At laparotomy performed shortly after admission an intussusception of the ileum was readily discerned. This was reduced easily, and the darkened color of the intestine improved promptly. A small dimple was seen on the serosa of the ileum at the origin of the intussusception. At this point a mass was palpable within the lumen from which a walnut-sized polyp was excised. The patient made a prompt and satisfactory recovery postoperatively.

Examination of the surgical specimen showed it to consist of a soft mucosa-covered papilloma with a small pedicle. The mucosa was intact and normal in appearance. The cut surface revealed a smooth, gray appearance. Microscopically, the specimen had the characteristics of a benign polyp.

CASE 5† A 9-year-old girl of Italian ancestry was admitted to the Children's Hospital of Boston on December 10, 1937, with the complaint of abdominal pain.

For the previous 2 years the child had had recurrent bouts of severe, crampy abdominal pains localized at the umbilicus.

*Reported through the courtesy of Dr. Francesco Ronchese of Providence, Rhode Island.

†This case and Figure 4 and 5 were made available through the courtesy of the Children's Hospital, Boston, Massachusetts.

They had never been associated with dietary indiscretions or irregularity of the bowels. The pains had been paroxysmal, lasting a few minutes and recurring in a few minutes, usually disappearing entirely after 1 or 2 hours. Occasionally, vomiting had been present with these episodes, but no bloody, tarry or mucus-containing stools had been noted. Typically, the patient was well immediately before and immediately after each attack, and on examination by various physicians and at outpatient clinics after an attack no abnormality had been found.

One hour before this hospital admission the patient again suffered a typical recurrence of crampy abdominal pain, which differed only in that it seemed much more severe than on previous occasions. Instead of disappearing, this pain kept recurring in stronger paroxysms every 1 or 2 minutes, making the child scream with pain. A few minutes after the



FIGURE 5 Close-up Photograph in Case 5, Showing the Density of the Melanin Spots on the Lips and about the Mouth

onset of this illness she began to vomit bile-stained material. Nothing was passed by rectum.

The patient had been a full-term, normal baby. She had been examined on several occasions in the Outpatient Department during the preceding 3 years for attacks of bronchitis and after previous attacks of abdominal pain. The past history was otherwise noncontributory. Her parents were living, the mother (Case 4) had undergone an abdominal operation for intussusception 2 years previously. One brother, 8 years of age, was living and well. Another sibling had been born dead 11 years previously. The patient's mother, and the latter's father and paternal grandmother had all had similar pigmentation of the face about the mouth. Unfortunately, information concerning polyposis in these ancestors was unobtainable.

Physical examination revealed an acutely ill girl. There were numerous blue-brown to black small spots on the face, concentrated about the mouth and on the mucosa of the lips and mouth (Fig 4 and 5). The hair and irides were dark brown. Examination of the heart and lung was negative. The abdomen was not distended, but there was moderate fullness in the left upper quadrant. No direct spasm could be elicited, but intermittently there was tenderness over a transiently palpable tumor in the left upper quadrant. This tumor appeared to be fairly movable in all directions and measured 10 by 5 cm. The liver edge was felt 1 cm below the costal margin. Rectal examination was negative. The white-cell count on entry was 20,150.

Shortly after examination a laparotomy was performed. A jejunoileal intussusception was promptly noted and was reduced. A walnut-sized tumor could be palpated at the site of intussusception, and on opening of the intestine a polyp was removed. *Staphylococcus aureus* septicemia, with pneumonia, empyema and peritonitis developed, and the patient died on January 2, 1938.

At autopsy, in addition to the pigmentation previously noted, there was a generalized petechial eruption. Bilateral bronchopneumonia and empyema were present. The abdominal cavity contained a large amount of brown fluid.

The mucosa of the stomach was thrown up into prominent longitudinal rugae, and on the tips of these rugae four polypoid formations were noted. These varied from mere mucosal elevations to one pedunculated polyp 2 cm in diameter, they were pinkish white and slightly lobulated. The entire small intestine contained numerous polyps of varying size, most of them about the size of a pea and many with pedicles, but occasional ones showing a sessile type of base. These were attached to the intestinal villi. The appendix was 10 cm long, with a reddish-black, bulbous tip. It was retrocecal in position and bound down in an appendiceal abscess. There was no abnormality of the large intestine. The mucosa of the rectum contained a polyp about 2 cm in diameter. A total of twenty polyps of the gastrointestinal tract were counted. The adrenal glands were normal in shape and consistency, the cut surface revealed a normal architecture. There were multiple small cysts of the left ovary, approximating 2 or 3 mm in diameter, and filled with clear, yellow fluid.

Examination of the polyp removed at operation showed it to be 4.3 by 3 by 1.8 cm. Cut section revealed a circular core, which was composed of tough connective tissue. Surrounding this was an abundant amount of glandular tissue. The mucosal epithelium was normal histologically. The lamina propria was markedly vascular, and there was extensive inflammatory cell infiltration consisting about equally of neutrophilic and eosinophilic polymorphonuclear leukocytes, plasma cells and mononuclear cells. At no part of the specimen was there any evidence of cancer.

CASE 6 A 16-year-old Negro boy born on the Outside Obstetrical Service of the Johns Hopkins Hospital had been observed throughout his life at frequent intervals in the various outpatient clinics and on the wards of the Johns Hopkins Hospital.

As far as could be determined the family history was negative for bowel difficulties and for pigmentation of the type under discussion.

The patient had suffered all his life from complications attributed to intestinal polyposis. At the age of 8 months rectal prolapse with a visible polyp had occurred. This recurred repeatedly in spite of removal of several polyps—described grossly and histologically as "papilloma of the rectum."

At the age of 6 years, the boy began to have attacks of periumbilical pain about once a month. In 1946 he was admitted to the hospital for intussusception. A laparotomy was performed by Dr. H. William Scott, Jr. An ileocolic type of intussusception was found. Taxis was unsuccessful. Resection of the ascending colon, half the transverse colon and the ileum back 30 cm from the beginning of the intussusception was performed. The ends of the colon and ileum were exteriorized by the Mickulicz technic and later closed. Two polyps were noted in the ileal portion of the operative specimen. There was no sign of melanosis coli in the specimen.

At the third admission, on June 11, 1947, because of dizziness and shortness of breath on exertion, the patient's diet was found to have been unusually inadequate, having consisted largely of candy and soft drinks. Physical examination revealed pallor and blowing systolic murmurs at the apex and in the pulmonic area. Examination of the blood disclosed a red-cell count of 3,420,000, with a hemoglobin of 4.3 gm, and a hematocrit of 19 mm, giving a mean corpuscular volume of 56 cubic microns, a mean corpuscular hemoglobin of 13 micromicrogm and a mean corpuscular hemoglobin concentration of 23 per cent.

The stools gave negative to +++++ guaiac tests. No parasitic ova or cysts were identified. Preparations for sickling were repeatedly negative. After a detailed gastrointestinal study it was finally concluded that the patient probably had polyps somewhere in the alimentary canal, which our imperfect methods could not demonstrate, and that bleeding from these, together with a grossly inadequate diet, was responsible for the anemia. Lack of absorptive surface as a result of extensive intestinal resection was a possible additional factor. On iron therapy the reticulocytes rose to a peak of 12.8 per cent.

It was on this admission that attention was called to the pigmentary peculiarities and studies thereof were made. On the outside of both lips and extending onto the skin about 1.5 cm from the vermilion border there were darkly pigmented spots of irregular outline and size varying from that

of a pinhead to 2 mm in the largest dimension (Fig 6). They covered the vermillion portions and the entire dental surfaces of the lips. There were a few similar spots on the buccal mucous membranes and lateral edges of the tongue. On the mucous membrane covering the posterior commissure of the upper and lower jaws there was on each side a prominent spot measuring about 4 mm in diameter (Fig 7). The general color of the skin was a very light tan. In the 'butterfly area' of the face there were also a few spots resembling those on the lips (Fig 6). There was a fleck of pigment in the bulbar conjunctiva of the right eye at the limbus at 8 o'clock, and a similar but small spot on the conjunctiva of the left eye at the limbus at 4 o'clock. Fundusoscopic examination revealed nothing remarkable. On the hypothenar

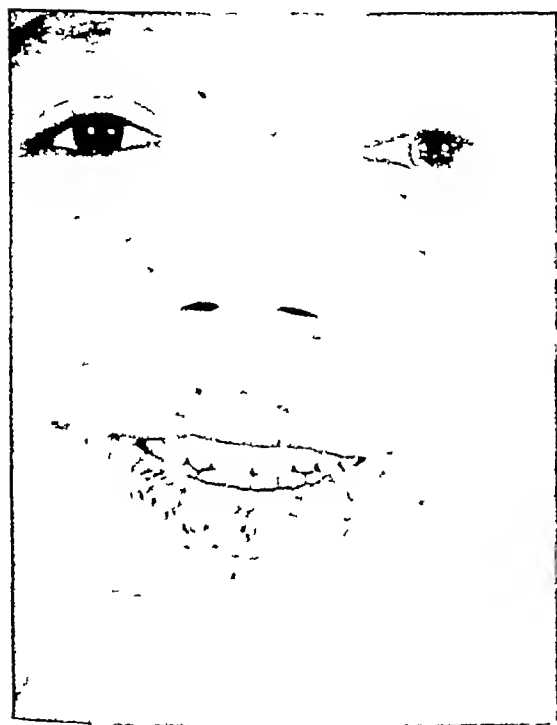


FIGURE 6 Appearance of the Patient in Case 6
The characteristic dense localization of spots on the lips, more marked on the lower lip, is well demonstrated. Note the relative paucity of spots elsewhere on the face.

eminence of the right hand there was a pigmented spot 5 mm in diameter. On both index fingers were numerous dots and under the nail of the left index finger at the point a pigmented area (Fig 8). There was a pigmented macule on the sole of the left foot. Otherwise the body was essentially free of any localized areas of increased pigmentation. All the areas described were not elevated and were perfectly smooth. These areas of pigmentation had been present as long as the patient or his mother could recall and had not changed. Unfortunately, no photographs from infancy or childhood were available. One brother and 2 half sisters did not show the anomaly. None of the mother's family showed it, the father's family lived in a distant state and was not available for observation.

On May 25, 1948, the patient was admitted again with intussusception. On that date a laparotomy was performed by Dr Marshall C Sanford. Two groups of polyps were palpated in the small intestine: one in the upper jejunum

just below the ligament of Treitz, the region being intussuscepted into the jejunum below for a distance of 21 cm, and a second group of polyps approximately 61 cm distal to Treitz's ligament. The jejunum was resected from the ligament of Treitz to below the second group and an end-to-end



FIGURE 7 Photograph Demonstrating Melanin Areas Inside the Mouth in Case 6

duodenojejunostomy performed. At this laparotomy a polyp was felt in the descending colon, and another in the sigmoid about 15 cm below the first. After proper prepara-

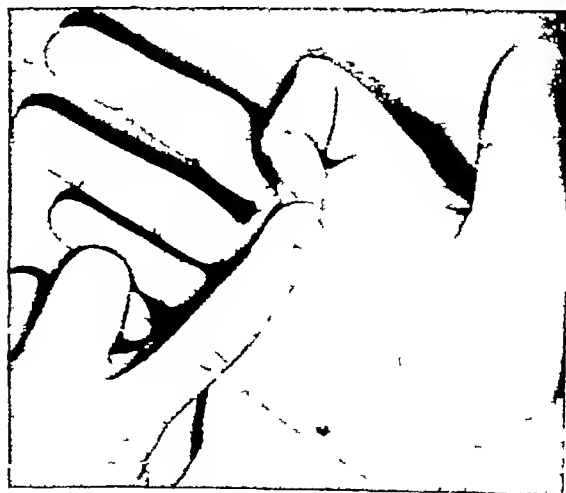


FIGURE 8 Photograph of the Right Hand in Case 6
Melanin spots are present on the palm and thumb and especially on the forefinger.

tion of the bowel with sulfasuxidine, a 15-cm length of the left colon including the polyps, was resected as a separate procedure on June 7. The polyps were grossly and microscopically identical with those previously removed.

CASE 7 * A 15-year-old girl had previously been admitted to the Johns Hopkins Hospital in 1937 at the age of 6 years. Eighteen months before that admission the patient had become rundown, pale and anorexic. One year before admission tarry stools were occasionally noticed, and there was the onset of dull abdominal pain present each morning on awakening. This daily morning pain continued until the time of the first admission, and, in addition, there was occasional nausea and vomiting. Sometimes, the pain required morphine for relief. During severe attacks it radiated to the left lower quadrant, where there was said to be a visible mass, and gurgling sounds were audible across the room. The stools were guaiac positive on numerous occasions, and the hemoglobin at one time was 30 per cent of normal.

On admission in 1937 the physical examination was recorded as essentially negative, and the diagnostic impression was Meckel's diverticulum. The spots in the mouth were described, but their diagnostic significance was not appreciated. Two days after admission the patient was seized with severe abdominal pain, which caused her to scream and clutch her abdomen. This was associated with continuous retching. On laparotomy 2 ileocecal intussusceptions and 3 polyps were discovered. The first intussusception was 45 cm above the ileocecal valve and was easily reduced. A polyp was palpated at the head of the intussusception and was removed by elliptical resection. About 76 cm above this intussusception was a second, larger one, which on reduction was found to be an intussusception within an intussus-

drop in hemoglobin to 60 per cent was observed. There was considerable nausea but no vomiting. Two days before, the patient had pain all day associated with considerable nausea but no vomiting.

On admission the physical findings were not remarkable except for the pallor (the hemoglobin was 9 gm) and the spots described below. There was no digital clubbing. The stools were brown and formed, but guaiac positive. Sigmoidoscopic examination, performed by Dr J T Howard, revealed 2 polyps in the lower sigmoid, 1 "the size of a peanut and the other the size of a hazelnut." A gastrointestinal series revealed negative filling defects in the stomach suggestive of polyps. Studies of the small intestine were performed by the passage of barium and then air through a Miller-Abbott tube inserted for the proper distance. By this method several areas suspicious of polyps were visualized. A barium enema by the routine technic and without injection of air was negative.

At operation, performed on October 31 by Dr I R Trimble, the stomach was opened, and 2 polyps were found on the greater curvature in the lower portion of the organ. The larger of these measured about 2 cm in diameter. The entire length of the small intestine was carefully examined by means of palpation and transillumination. In the distal jejunum and proximal ileum several polyps were palpated, and about 122 cm of this portion of the gut was resected. This specimen contained 8 large pedunculated polyps, the largest of which measured about 25 cm in diameter. Histologic examination revealed these structures to be typical benign polyps. Several polyps could be palpated in the transverse colon (the only portion of the large intestine in the operative field), but no operative procedure was attempted in connection with them.

The patient was an only child. Absolutely no history of gastrointestinal disturbance could be elicited among her forebears, nor had any of them, including the parents, shown a pigmentary anomaly resembling the patient's. These spots had been noted almost from birth. There was no family history of freckles. The mother had a photograph of the patient at the age of 3 months showing them quite distinctly. These spots were numerous on the vermilion border and on the dental aspect of the lips. They were perfectly flat areas of hyperpigmentation of irregular outline and variable size. On examination with a magnifying glass some of the spots had a somewhat stippled appearance. Spots of the same description were present on the buccal mucous membrane (Fig 9) bilaterally, but none were seen on the tongue. There were several light spots over the palms and fingers, and there were a few on the feet. The remainder of the body was completely free of any unusual type of pigmentation. No freckles were present—in fact, the skin of the face was exceptionally free of all blemishes except the melanin spots described above.

CASE 8 † A 27-year-old man, second in a family of five the genealogy of which is shown in Figure 10, was a brother of the patients in Case 9 and 10. He was born in 1921. From an early age he has been subject to frequent, in fact almost daily "belly aches," especially after eating. Over the course of about 18 months, in 1938 and 1939, at the age of about 17, he had had some very severe attacks of crampy, intermittent abdominal pain, for which he was admitted to the Harrisburg Hospital on several occasions. Each time, the pain disappeared spontaneously and no satisfactory diagnosis was arrived at. Finally, the possibility of intestinal polyposis, with intussusception, was proposed by Dr C E Moore, who performed a laparotomy on December 18, 1939. At that time an easily reducible intussusception in the upper portion of the jejunum was discovered, and multiple soft masses could be felt in its lumen. About 150 cm of jejunum was resected extending from 10 cm below the ligament of Treitz to below the area where polyps could be felt. End-to-side anastomosis was necessary because of luminal disproportion. The specimen removed was described by the pathologist as showing 30 soft, lobulated polyps. Microscopically, they were the usual adenomatous polyps.

Early in 1945, attacks of crampy abdominal pain began, mainly on the right, increasing in severity and frequency over the course of 3 months. On January 16, 1948, because of these increasingly severe attacks, laparotomy was per-



FIGURE 9 Appearance of the Patient in Case 7

Note the spots on the lower lips and on the buccal mucosa. Spots are also visible on the mucosa just inside the nostril. Spots on the upper lip are relatively sparse.

ception with a polyp as the cause of each invagination. These polyps were similarly resected. No others were found.

The patient did well until the following spring, when she had an acute attack of abdominal pain and was operated upon in a South Carolina hospital, where adhesions were reported as the only finding. Thereafter she was well until 1946. During the next year there was a gradual loss of appetite, development of weakness and a loss of about 6 pounds of weight. Two months before this admission the old crampy abdominal pain recurred lasting from 1 to 12 hours at a time. In the 2 weeks before admission in October, 1947, a steady

*This case is reported with the permission of Dr I R Trimble. A report of this case is included in the paper by Ravitch¹⁸ dealing with polyoid adenomatosis of the entire gastrointestinal tract.

†Case 8, 9 and 10 are reported through the courtesy of Dr C F Moore of Harrisburg, Pennsylvania.

formed. Two intussusceptions were discovered. The first was 90 cm proximal to the ileocecal valve, with telescoping of the bowel for 10 cm. At the head of the intussusception was a thumb-sized polyp, which was removed by simple elliptical incision. The second intussusception was ileocolic in type and had its cause, again, in a small polyp the size of an English walnut. This was removed in a similar manner. A very careful examination of the entire gastrointestinal tract was made. No evidence of polyps was found in stomach, duodenum or jejunum, and on this occasion none could be felt in the colon, including the transverse colon where it was thought that a solitary one had been felt in 1943. Histologically, the polyps were not remarkable.

After this operation the patient was asymptomatic up to the time when he was examined by one of us. He was found to be a very muscular young man, perhaps slightly

CASE 9 The sister (born in 1924) of the patients in Case 8 and 10, was 4th in a family of 5, the genealogy of which is shown in Figure 10. Through early adolescence the patient had suffered from recurrent attacks of crampy abdominal pain accompanied at times by vomiting. There was never melena or fresh blood in the stools, and she was never noticeably anemic. At the age of 16, because of this history and because of the previous discovery of polyposis in a brother (Case 8) she was admitted to the Harrisburg Hospital, and laparotomy was performed on June 28, 1940, by Dr C E Moore. The upper 91 cm of the jejunum was found to be somewhat dilated, and many firm nodules were palpated in its lumen, the most proximal one being about 5 cm below the ligament of Treitz. No intussusception was present at the time of laparotomy. The stomach, duodenum, ileum and colon appeared to be normal. The proximal 90 cm

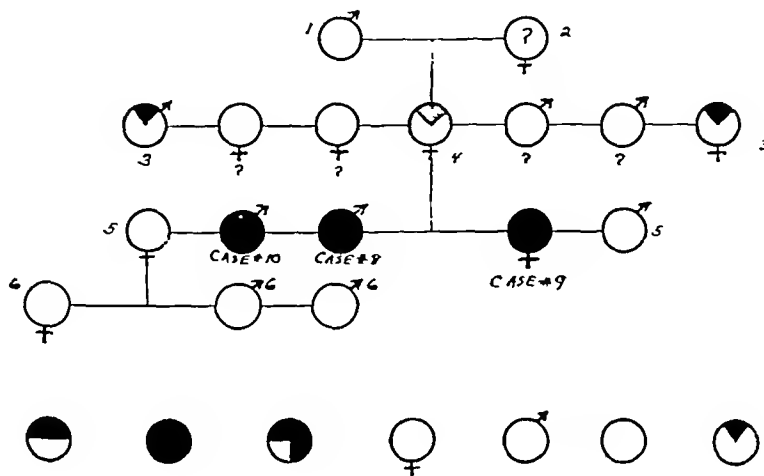


FIGURE 10 Genealogic Table of Harrisburg Family with Pigment Spots and Polyposis (Data Provided through the Courtesy of Dr C E Moore)

Key: Blank circle = normal. One-fourth circle = pigmentation not looked for, probable polyposis. One-half circle = pigmentation, no polyps clinically. Three-fourths circle = pigmentation and probable polyposis. Full circle = pigmentation and proved polyposis.

1 Death from cancer of pancreas at age of sixty-nine. No pigmentation or intestinal polyps at autopsy.

2 No information available except death from "heart attack."

3 Death from "intussusception" in second decade of life. No information about pigmentation.

4 Death from "cancer of intestine" at age of forty. No information about pigmentation.

5 No history of pigmentation or intestinal trouble. Not available for examination (See footnote under Case 10).

6 No history of pigmentation or intestinal trouble. Not available for examination (See footnote under Case 10).

? No information available.

overweight. There was no evidence of anemia. The eyes were dark blue, and the hair brown black. The only unusual feature of the examination was the presence of gray pigmented spots on the vermilion border of the lower lip identical with those in the other cases. The spots were concentrated somewhat toward the commissure on either side. There were no spots on the dental aspects of the lips but on the buccal mucosa in the region of the posterior commissures of the jaw and in juxtaposition to the lower teeth there were small, irregular spots, which had a definite stippled appearance on magnification. There were two spots likewise stippled, on the hard palate (These spots had been noted from the first by Dr Moore, who speculated on their possible relation to the intestinal polyposis). The face, which was deeply sun-tanned was essentially free of freckles. The hands were rough and calloused, but a few small, brown-gray spots were seen on both dorsal and volar aspects of the fingers. The spots on the lips had been present and unchanged as long as the patient could recall.

of the jejunum was resected and the continuity was restored by a lateral anastomosis. The specimen was found to contain 5 polyps, the largest measuring 3.5 cm in length and 2.2 cm in diameter. Histologically, they were the usual polypoid adenomas.

After operation the patient was asymptomatic. When examined by one of us in 1948 she was well developed and adequately nourished without evidence of anemia. She was somewhat darker in complexion than her brothers. The hair was black and the irides dark brown. The only unusual feature of the physical examination consisted of dark pigmented spots on the vermilion border of the lower lip, with a few smaller ones on the cutaneous portion of the lower lip. Those on the vermilion border were quite deeply pigmented and prominent, and only imperfectly concealed by lipstick. In the mouth there were 2 spots on the left buccal mucosa, 3 on the right and a single small pigmented area on the hard palate. All these areas had a definitely stippled appearance. There were a few spots in the butterfly area of the nose and

CASE 7* A 15-year-old girl had previously been admitted to the Johns Hopkins Hospital in 1937 at the age of 6 years. Eighteen months before that admission the patient had become rundown, pale and anorexic. One year before admission tarry stools were occasionally noticed and there was the onset of dull abdominal pain present each morning on awakening. This daily morning pain continued until the time of the first admission, and, in addition, there was occasional nausea and vomiting. Sometimes, the pain required morphine for relief. During severe attacks it radiated to the left lower quadrant, where there was said to be a visible mass, and gurgling sounds were audible across the room. The stools were guaiac positive on numerous occasions, and the hemoglobin at one time was 30 per cent of normal.

On admission in 1937 the physical examination was recorded as essentially negative, and the diagnostic impression was Meckel's diverticulum. The spots in the mouth were described, but their diagnostic significance was not appreciated. Two days after admission the patient was seized with severe abdominal pain, which caused her to scream and clutch her abdomen. This was associated with continuous retching. On laparotomy 2 ileoileal intussusceptions and 3 polyps were discovered. The first intussusception was 45 cm above the ileocecal valve and was easily reduced. A polyp was palpated at the head of the intussusception and was removed by elliptical resection. About 76 cm above this intussusception was a second, larger one, which on reduction was found to be an intussusception within an intussus-

drop in hemoglobin to 60 per cent was observed. There was considerable nausea but no vomiting. Two days before, the patient had pain all day associated with considerable nausea but no vomiting.

On admission the physical findings were not remarkable except for the pallor (the hemoglobin was 9 gm) and the spots described below. There was no digital clubbing. The stools were brown and formed, but guaiac positive. Sigmoidoscopic examination, performed by Dr J T Howard, revealed 2 polyps in the lower sigmoid, 1 "the size of a pea nut and the other the size of a hazelnut." A gastrointestinal series revealed negative filling defects in the stomach suggestive of polyps. Studies of the small intestine were performed by the passage of barium and then air through a Miller-Abbott tube inserted for the proper distance. By this method several areas suspicious of polyps were visualized. A barium enema by the routine technic and without injection of air was negative.

At operation, performed on October 31 by Dr I R Trimble, the stomach was opened, and 2 polyps were found on the greater curvature in the lower portion of the organ. The larger of these measured about 2 cm in diameter. The entire length of the small intestine was carefully examined by means of palpation and transillumination. In the distal jejunum and proximal ileum several polyps were palpated, and about 122 cm of this portion of the gut was resected. This specimen contained 8 large pedunculated polyps, the largest of which measured about 25 cm in diameter. Histologic examination revealed these structures to be typical benign polyps. Several polyps could be palpated in the transverse colon (the only portion of the large intestine in the operative field), but no operative procedure was attempted in connection with them.

The patient was an only child. Absolutely no history of gastrointestinal disturbance could be elicited among her forebears, nor had any of them, including the parents, shown a pigmentary anomaly resembling the patient's. These spots had been noted almost from birth. There was no family history of freckles. The mother had a photograph of the patient at the age of 3 months showing them quite distinctly. These spots were numerous on the vermillion border and on the dental aspect of the lips. They were perfectly flat areas of hyperpigmentation of irregular outline and variable size. On examination with a magnifying glass some of the spots had a somewhat stippled appearance. Spots of the same description were present on the buccal mucous membrane (Fig 9) bilaterally, but none were seen on the tongue. There were several light spots over the palms and fingers, and there were a few on the feet. The remainder of the body was completely free of any unusual type of pigmentation. No freckles were present—in fact, the skin of the face was exceptionally free of all blemishes except the melanin spots described above.



FIGURE 9 Appearance of the Patient in Case 7

Note the spots on the lower lips and on the buccal mucosa. Spots are also visible on the mucosa just inside the nostril. Spots on the upper lip are relatively sparse.

ception with a polyp as the cause of each invagination. These polyps were similarly resected. No others were found.

The patient did well until the following spring, when she had an acute attack of abdominal pain and was operated upon in a South Carolina hospital, where adhesions were reported as the only finding. Thereafter she was well until 1946. During the next year there was a gradual loss of appetite, development of weakness and a loss of about 6 pounds of weight. Two months before this admission the old crampy abdominal pain recurred, lasting from 1 to 12 hours at a time. In the 2 weeks before admission in October, 1947, a steady

CASE 8† A 27-year-old man, second in a family of five the genealogy of which is shown in Figure 10, was a brother of the patients in Case 9 and 10. He was born in 1921. From an early age he has been subject to frequent, in fact almost daily, "bellyaches," especially after eating. Over the course of about 18 months, in 1938 and 1939, at the age of about 17 he had had some very severe attacks of crampy, intermittent abdominal pain, for which he was admitted to the Harrisburg Hospital on several occasions. Each time, the pain disappeared spontaneously and no satisfactory diagnosis was arrived at. Finally, the possibility of intestinal polyposis, with intussusception, was proposed by Dr C E Moore who performed a laparotomy on December 18, 1939. At that time an easily reducible intussusception in the upper portion of the jejunum was discovered, and multiple soft masses could be felt in its lumen. About 150 cm of jejunum was resected, extending from 10 cm below the ligament of Treitz to below the area where polyps could be felt. End-to-side anastomosis was necessary because of luminal disproportion. The specimen removed was described by the pathologist as showing 30 soft, lobulated polyps. Microscopically, they were the usual adenomatous polyps.

Early in 1945, attacks of crampy abdominal pain began, mainly on the right, increasing in severity and frequency over the course of 3 months. On January 16, 1948 because of these increasingly severe attacks, laparotomy was per-

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†Case 8, 9 and 10 are reported through the courtesy of Dr C F Moore of Harrisburg, Pennsylvania.

first twin. A recent personal communication from R. H. (a living brother of the twins) states that the second twin died at the age of fifty-two of cancer of the breast. He could supply no data concerning intestinal symptoms. She died at home, and no autopsy was performed. Weber¹ noted no pigmentation in the other members of the twin's family, a point corroborated by the brother, R. H.

Case 3 was called to our attention by Dr. Francesco Ronchese, of Providence, Rhode Island, after publication of the preliminary note concerning Case 1 and 2.¹

The patient in Case 4, a first cousin of another patient (Case 2), and still alive, came to our attention when relatives of the latter were questioned

and intestinal polyposis by a specific title is a paper by Peutz,⁷ of The Hague, who, in 1921, described a family in which several members had pigment spots of the mouth, hands and feet with intestinal polyposis. Reference to this paper is made by Meirowsky,⁸ and the article is also listed in the *Index Medicus* but was overlooked in our earlier, limited search.

No other title under the heading of intestinal polyposis with pigmentation was found in the *Quarterly Cumulative Index Medicus* or *Index Medicus* prior to 1945. Metzger, Ohlmann and Halff,⁹ under another title, reported a case of polyposis with a diffuse type of generalized melanin pigmentation that did not resemble the appearance

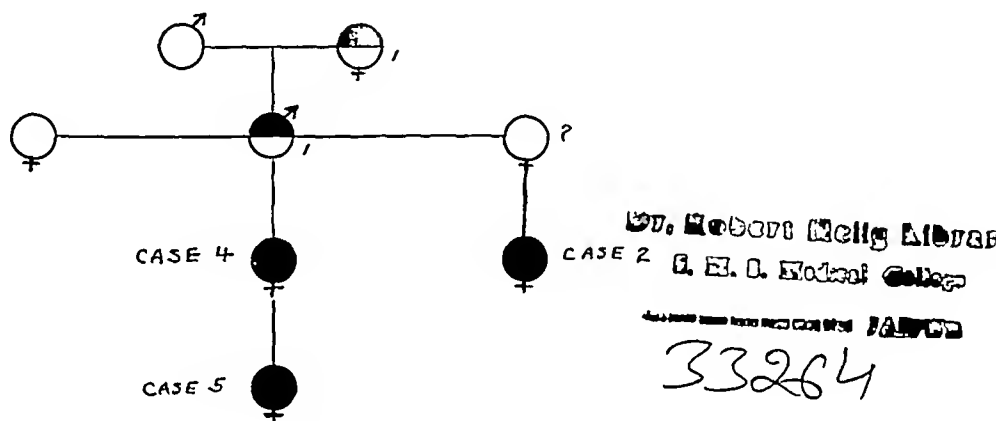


FIGURE 12 Genealogic Table of Boston Family with Pigment Spots and Polyposis

1 Known to have characteristic pigmentation. No information about polyposis available.
2 No information available.

about her family history. She had been admitted to Boston City Hospital in 1935. Adequate data were available in this record.

The patient in Case 4 gave the details for assembling the pedigree of the syndrome in this family (Fig. 12) and led to knowledge of her daughter (Case 5), who had died at the Children's Hospital, Boston, Massachusetts, in 1938.

Case 6 and 7 were noted by one of us at the Johns Hopkins Hospital within a few months of each other.

Cases 8, 9 and 10 are patients of Dr. C. E. Moore, of Harrisburg, Pennsylvania, who, hearing of our interest in this syndrome, called them to our attention and permitted one of us to examine them.

The finding of 10 patients with this syndrome stimulated us to a more thorough search of the literature than the one made in 1944, when Case 1 and 2 were reported briefly.

Apparently the first specific reference in the medical literature concerning this disorder and the earliest to stress the association of pigmentation

in our cases. No mention of this syndrome was found in a representative group of standard textbooks on gastrointestinal disease, or in the standard dermatologic textbooks in English. This does not exclude the possibility that representative cases are reported under titles that would not suggest this syndrome.

As previously stated, Peutz,⁷ of The Hague, in 1921, described a family in which several members had pigmented spots of the mouth, hands and feet. Dr. Peutz¹⁰ has very kindly supplied us with further information on this family, permitting the construction of the fabulous family tree shown in Figure 13. The cases cover three generations, with seven proved cases of the syndrome (intestinal polyps and spots), 1 suspected case and 1 person who presented the pigmentary anomaly without proved polyposis. Two of the family had nasal polyps in addition to the intestinal polyps, and 1 also had bladder polyps.

Figure 14 demonstrates the spots on the dental aspect of the lower lip in 1 of the cases (No. 7 in

cheek. On both the dorsal and volar aspects of the fingers were a number of brown spots. The remainder of the body was free of unusual pigmentation.

CASE 10 The brother of the patients in Case 8 and 9 and 2nd in a family of 5, the genealogy of which is shown in Figure 10, experienced, at about the age of 20, recurrent attacks of mid-abdominal pain occurring especially between 1 and 2 hours after eating and occasionally accompanied by vomiting. The attacks increased in severity and frequency over the course of the next 2 years. In 1942 he was admitted to the Harnsburg Hospital with a particularly severe attack of this description of 2 days' duration. An indefinite tumescence was observed in the region of the umbilicus. At laparotomy, performed on February 16, by Dr C E Moore, an intussusception was found in the jejunum about 76 cm below the ligament of Treitz. This was quite easily reduced. At the head of the intussusception a polyp was palpated, and several others were felt in the jejunum to a distance of 122 cm from the ligament of Treitz. The stomach, duodenum, ileum and colon felt normal. The jejunum was resected for a distance of 122 cm, beginning at a point 15 cm below the ligament of Treitz. Lateral anastomosis was performed, the continuity of the bowel thereby being re-established.

After operation the patient had been completely asymptomatic up to the time he was examined by one of us in 1948. At that time he was found to be a very muscular, slightly overnourished young man with good color and a striking resemblance to his younger brother. The hair was dark brown, and the irides dark blue. In this case, the pigmentation of the lips was the least marked of any of the siblings. There were, however, over the vermilion border of the lower lip, 10 or 12 small dark-brown, pigmented spots concentrated mainly near the commissure on either side. Inside the mouth there were 2 or 3 pigmented spots with a stippled appearance on the buccal mucosa on each side. There was no pigmentation of the hard palate. The face was deeply tanned, but essentially free of freckles. The hands were calloused and roughened, but showed a few spots on the fingers.*

REVIEW OF THE LITERATURE

Interest in this syndrome was first aroused when a patient (Case 1) was seen on the Fifth Medical



FIGURE 11 Identical Twins, Each with Melanin Spots on and about the Lips and on the Buccal Mucosa, as Shown in the Small Insert (Reproduced from Hutchinson²)

Note the similarity of distribution of pigment spots in these cases with those reported in this paper

Service of the Boston City Hospital in 1939 during a study of the association of skin pigmentation with systemic disease.¹ Dr Chester S. Keefer, who

*On January 22, 1949, the youngest member of this Harnsburg family, a 21-year-old man, died a few days after admission to another hospital for an acute abdominal episode. Two operations were performed at which the intussusception due to polyp of the small intestine was discovered. The brothers and sisters of this patient stated that he showed no pigmented spots, but he was actually not examined by us.

had seen the patient on ward rounds, commented later, in a personal communication, on the similarity of this girl's pigmentation to that of twins in the cases reported by Sir Jonathan Hutchinson² in 1896. This report concerned twelve-year-old twins (Fig. 11) with an anomaly described as follows:

a number of black pigmented spots on the lips and inside of the mouth. It was at the age of three that these spots had first been noticed, and the evidence was definite that none had been present at birth. The spots had increased in number and size at exactly parallel rates in the two, and the conditions presented were just the same in each.

No note is made of the presence or absence of pigmented areas on the hands. The striking resemblance between the pigmentary pattern in Case 1 and the twins described by Hutchinson is clearly demonstrated by comparison of Figure 1 and Figure 11.

Hutchinson was not aware of the presence of any intestinal trouble in either of the twins, for he wrote further: "That they [the pigmented spots] are not in any active sense pathological we may safely assure, for they appear to be not aggressive, and their subjects remain in good health." Because of the marked similarity of the process in the twins, Sir Jonathan considered the pigmentation a congenital anomaly.

A brief note on these twins had previously been published by Connor,³ who contributed the significant additional information that the twins were "of dark complexion and anemic." The pigment spots were described as being "of very small size and scattered over the lips (especially the lower), gums and hard palate, but not on the tongue."

The patient in Case 2 was seen at Boston City Hospital later in 1939 and because of similarity to Case 1 was likewise photographed and studied. This second case strongly suggested that this distinctive type of pigmentation in combination with intestinal polyposis was not a fortuitous association but was probably of related significance.

A limited search of the literature at that time revealed a paper by Weber,⁴ who in 1919 reported a follow-up study on Hutchinson's cases. He stated that the spots apparently had not enlarged. However, the most interesting portion of his follow-up observation was this: "One of the twins died at the age of twenty years, from intussusception, at the Metropolitan Hospital (London), but the other (B. H.) is still living and is in good health, now (1919) aged thirty-five years." The Metropolitan Hospital⁵ has no record that an autopsy was performed, a point confirmed by Weber.⁶ However, from a copy of the death certificate obtained for us by Dr L. Forman, British dermatologist, it is known that an operation for intussusception with resection of the gut was performed and that the patient died of "septic pneumonia and pleuritis." Although not specifically stated, there is a strong possibility that intestinal polyposis was the cause of the intussusception in the

obtained from Kisch,¹³ who reports that his original notes are no longer available. However, he confirmed the validity of the statement of Meirowsky.

Four proved and 2 probable cases of this syndrome came to our attention while we were reviewing the quite limited literature of familial adenomatosis of the small intestine.

In 1924 van Dijk and Oudendal¹⁴ from Weltevreden in the Dutch East Indies, reported the cases of a sixteen-year-old Indo-European boy and his twenty-five-year-old sister, both of whom suffered from repeated colicky attacks. During severe attacks both were submitted to laparotomy and found to have intussusception of the ileum due to adenomas. Both patients showed pigmented spots of the lips which had been present from birth and which resembled those found in our patients. The au-

been a patient in this hospital in 1935 complaining of attacks of abdominal pain, with the passage of blood and mucus per rectum." The subsequent course of events was as follows:¹⁶ "This man was admitted to a nearby hospital in Cardiff during 1947 and laparotomy then showed an inoperable carcinoma of the stomach. No further history is obtainable at the moment."

Foster¹⁶ supplied information on a fourth very likely case of the syndrome in this Welsh family:

[The son of the patient just described] was admitted to Llandough Hospital on the 7th of October 1944, as a case of Addison's disease apparently on account of the pigmentation of the lips, oral mucous membrane, and

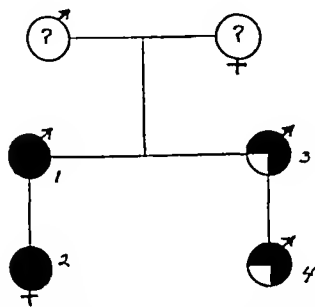


FIGURE 15 Genealogic Table of a Welsh Family with Pigment Spots and Polyposis (Based on Data of Foster¹⁶ 15)

1 Forty-three-year-old silversmith with spots and a proved polyposis of the ileum

2 Fifteen-year-old girl with spots and a proved polyposis of the ileum

3 Had the characteristic pigmentation and passage of blood and mucus by rectum. Inoperable carcinoma of the stomach developed

4 Has the characteristic pigmentation as well as frequent attacks of colicky abdominal pain with passage of blood and mucus

No information available

thors did not mention Peutz's publication of 1921 and did not stress the significance of the association of pigmented spots and intestinal polyposis.

In 1944 Foster¹⁵ reported the cases of a forty-three-year-old silversmith and his sixteen-year-old daughter who presented themselves at the Llandough Hospital in Cardiff, Wales, within three years of each other with intussusception, which on laparotomy was found to be due to a single polyp. Foster stated "It was noted that both patients presented a diffuse brownish pigmentation of the lips and face." No further comment was made of the pigmentation. In reply to our inquiry Foster¹⁶ generously sent us a photograph of the daughter. The identity with the other cases is unmistakable.

In his report Foster¹⁵ stated "On investigating the family history it transpired that the father's brother showed similar pigmentation and he had



FIGURE 16 Appearance of a Patient with Melanin Spots (Reproduced from Touraine and Couder¹⁵ with the Permission of the Publisher)

This illustration clearly depicts the appearance of the melanin spots on the mucosa of the mouth

palate. A history of attacks of abdominal pain of a colicky nature, occasionally severe and associated with the passage of blood and mucus per rectum over a period of about nine months was obtained. Since then he has had occasional attacks of abdominal pain with the passage of some mucus per rectum.

Sufficient data were supplied by Foster for us to assemble a genealogic table for this family (Fig 15).

The only other report of the complete syndrome was made by Touraine and Couder,¹⁷ of Paris, in 1945, under the title "Syndrome of Peutz," and elaborated upon in 1946 under the title "Lentiginose péri-orificielle et polyposé viscérale."¹⁸ Their

Figure 13), together with the operative specimen from the ileum showing polyps. Although the face was more extensively involved in each of these

The first soot-coloured or dark-brown skin and lip pigmentation gradually faded in the course of years and even disappeared for the greater part between the ages of twenty-five and thirty, the spots got at least much

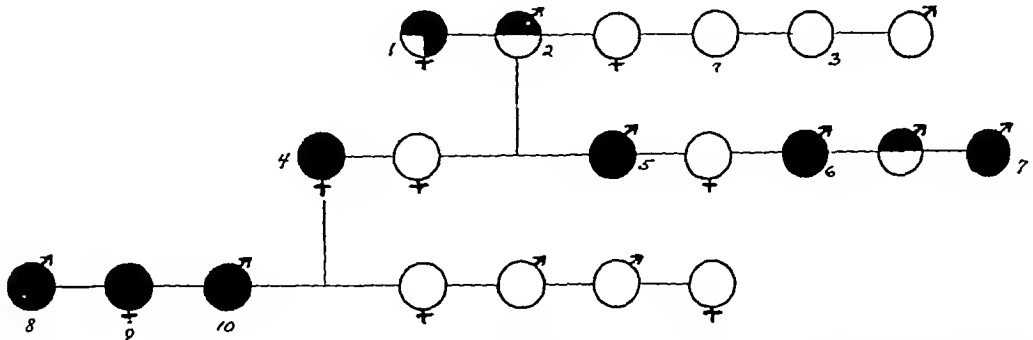


FIGURE 13 Genealogic Table of Dutch Family with Pigment Spots and Polyposis (Based on Data of Peutz^{7,10})

- 1 A nun — died of intestinal disease. History suggestive of polyposis. Had characteristic pigmentation.
- 2 Had characteristic pigmentation. Not studied for presence or absence of polyposis.
- 3 Died at age of four. No information available.
- 4 Several abdominal operations for intestinal polyposis. Died with ileus in 1937. Had characteristic pigmentation.
- 5 Had the pigmentation. Died with ileus in 1947. Malignant degeneration of intestinal polyps at autopsy.
- 6 Had the pigmentation. Died with ileus in 1948. Malignant degeneration of intestinal polyps at autopsy.
- 7 Case reported in detail by Peutz⁷ in 1921. Intestinal polyps and characteristic pigmentation. Malignant degeneration diagnosed on surgical specimen.
- 8 Died of ileus in 1940. Polyps previously proved by rectoscopy and x-ray studies. Had characteristic pigmentation.
- 9 Had polyposis of intestine and characteristic pigmentation.
- 10 Had polyposis of intestine and characteristic pigmentation.

cases than in our series the pigmentation of the lips and oral mucosa is identical. The extensive facial pigmentation is similar to that in the cases of Foerster¹¹ and Siemens¹² referred to below

smaller. The rectal and mouth pigmentation did not undergo this fading and becoming smaller [italics ours]

Foerster¹¹ and Siemens¹² have described a total of 5 cases demonstrating extensive spotty pigmentation of the skin, lips and oral mucosa. Four of the cases were in members of the same family. Although the distribution of pigment on the lips, oral mucosa and digits resembled that in our cases, the pigmentation on the skin was much more extensive. Furthermore, these patients were studied only from the dermatologic standpoint, and any evidence of intestinal polyposis, if present, was not included in the reports. It is not clear therefore, whether these patients fall in the group studied by Peutz and ourselves.

Foerster¹¹ suggested that this pigmentary anomaly may represent an atavism. Siemens¹² referred to the spots as "ephilides inversae" because they are located where freckles are not seen at all or are only very sparse. Siemens's terminology aptly fits the distribution of the pigment spots in the cases of Peutz and ourselves.

To some slight extent the syndrome may have been known in Germany. In Jadassohn's *Handbuch*,⁸ Meierowsky, in commenting on Peutz's cases, stated "Professor Bruno Kisch has observed a case which belongs in this group, there were pea-sized spots of the gums, the father had died of ileus, the grandfather had succumbed to obstipation." Unfortunately no further details can be



FIGURE 14 Surgical Specimen and Appearance of Patient in a Case of Pigment Spots and Polyposis (Reproduced from Peutz⁷ with the Permission of the Publisher)

On the left is a resected portion of the small intestine, showing polyps. On the right is a photograph of the patient showing pigment spot on the lips and face. Note that the spots on the face in this patient were much more numerous than those on the face in the cases reported by us.

Regarding changes of the pigmentation with aging of the subject, Peutz¹⁰ has the following interesting comment

The proved, probable and possible cases recorded in the literature or described in personal communications are summarized in Table 1

Although one of us has been looking for such cases for the past eight years, we have personally encountered only 1 case in which a pigment pattern indistinguishable from that of the syndrome being discussed in this paper was noted in a person in whom polyposis could not be demonstrated. A brief report of this case* is as follows

C L., a 57-year-old woman from Pueblo, Mexico, was seen at the Johns Hopkins Hospital because of precordial pain, and was examined by one of us. The family history was negative for pigmentation, but intestinal trouble was present in the form of "strangulated hernia" in the maternal grandfather, chronic indigestion in a brother and fatal gastric hemorrhage in the father.

The patient was an obese woman with hypertension and typical angina pectoris. Intestinal complaints were denied. The pigmented spots of the lips and oral mucosa, which were similar to those in our other cases and are shown in Figure 17, had been present for at least 8 years and possibly longer. This point, however, was not too clearly established. The spots were located on the vermilion border of the lower lip, to a less extent of the upper lip, on the buccal mucosa and on the hard palate. There were a few small light spots on the palms and volar aspects of the fingers, but none were seen on the feet. The spots in and around the mouth varied in dimension from pin-point size to about 6 mm in the largest measurement. They were brown black. On observation under magnification the spots had a definite, stippled appearance similar to that in Case 7, 8, 9 and 10.

Barium enema including a double contrast air study, was negative, as were an upper gastrointestinal study and sigmoidoscopy. The stools were negative for occult blood. No special small-bowel study was made.

Because of the absence of gastrointestinal symptoms and negative studies, it was concluded that the patient probably did not have intestinal polyposis.

*We are indebted to Dr. R. Carmichael Tilghman for calling this case to our attention and for permission to publish it.

(To be concluded)

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patient was a fifteen-year-old girl with pigment spots of the lips and buccal mucosa (Fig 16) The parents and a single sister were normal In addition to the typical pigmentation, the patient had habitual constipation and occasional rectal prolapse with defecation Rectal examination revealed an "enormous dilatation of the rectal ampulla and of the sigmoid, 7 cm from the anus there was a mobile polyp, the size of a large nut, which, on biopsy, was a simple adenoma with great dilatation of the glandular cavities but without neoplastic transformation" A study adequate to exclude small-bowel polyposis was not made so that one can only speculate on its possible existence

Touraine and Couder¹⁸ collected from the literature 31 cases of pigment pattern identical with that in the case described by them, by Peutz and by us The term "lentiginose péri-orificielle" was used to describe the pigment portion of the syndrome These cases occurred as follows 22 cases were familial, 8 occurred in three generations

TABLE 1 Cases of Intestinal Polyposis and Pigmentation

TYPE OF CASE	AUTHOR	REPORTED IN LITERATURE	REPORTED BY PERSONAL COMMUNICATION
		NO OF CASES	NO OF CASES
Proved	Peutz ⁷ 18	4	3
	van Dijk and Oudendal ¹⁴	2	
	Foster ¹⁴	2	
	Touraine and Couder ¹⁷ 18 (only rectal polyps identified)	1	
Probable	Twin described by Hutchinson ¹⁴ 18 (E. A. H.)		1
Possible	Peutz ⁷ 18	2	
	Foster ¹⁴ 18	1	1
	Twin described by Hutchinson ¹⁴ 18 (B. H.)	1	
	Crouzon and Chatelin ²²	1	
	Hudelo and Rabut ²³	1	
	Belote ²¹	1	
Totals		16	5

(Peutz⁷), 5 in four generations (Siemens¹²) and 9 in three generations (Ferrari¹⁹) Our original report of 2 cases was apparently not available to Touraine and Couder and not included by them in this tabulation (Its publication in a paper under the general title "Pigmentation of the Skin" made recognition through the index listing difficult) They likewise were not aware of Foster's¹⁴ cases or those of van Dijk and Oudendal,¹⁴ probably because of the misleading titles of these two papers As listed in this tabulation only the 4 cases of Peutz⁷ and possibly the one reported by Touraine and Couder^{17, 18} had the full syndrome

It is of interest that in these various reports of the pigment pattern collected by Touraine and Couder¹⁸ 3 patients had data suggesting polyposis Belote²⁰ reported at a dermatologic meeting the case of a twelve-year-old boy with the characteristic pigmentation who complained of bleeding from the rectum and increasing weakness, tarry stools

had been present occasionally, and examination of the blood demonstrated secondary anemia No further data on studies of the gastrointestinal tract were given Because of the death of Dr Belote it was impossible to trace this case further²¹

In 1912, Crouzon and Chatelin²² reported a case of the pigmentation in an eighty-three-year-old woman on the service of Pierre Marie at the Salpêtrière In addition to the identical pigmentation, the patient was said to suffer from "rather frequent



FIGURE 17 Photograph of a Fifty-Seven-Year-Old White Woman Who Had Melanin Spots of Lips and Mucous Membrane of the Mouth but in Whom Polyps of the Stomach or Colon Were Not Demonstrated

This is a possible case of pigmentary portion of the syndrome without polyposis

attacks of diarrhea (once or twice a month), not accompanied by vomiting"

The remaining suspected case of the syndrome was reported by Hudelo and Rabut²³ in 1927 Their patient manifested the characteristic pigmentation and in addition was said to have suffered from "indigestion, abdominal pains and nausea" Histologic study of a biopsy specimen revealed the pigment to be melanin

was readily mobilized and the vascular pedicle carefully isolated. The renal artery was small and no pulsations could be seen or felt. It was followed toward its origin until it disappeared beneath the vena cava without the demonstration of any pulsating portion. At the hilus of the kidney the artery divided into two main branches. One of these divisions was deliberately cut without clamping and a thin trickle of blood, with no pulsatile quality whatever to the flow, emerged. The artery was then clamped, cut and ligated and the veins similarly treated. The ureter was divided between ligatures and the kidney removed. The flank wound was closed in layers with drainage.

Postoperatively the blood pressure was carefully followed, and during the 9 days in the hospital after operation the systolic pressure varied from 100 to 120 and the diastolic from 60 to 80. Two weeks after discharge the blood pressure was 116/77 and on 9 subsequent occasions up to 17 months postoperatively has never been higher than 120/80 or lower than 110/70. The patient has remained well and vigorously active.

The kidney was subjected to careful pathological examination, and the following is the description of the organ by the pathologist*.

The specimen consists of a right kidney measuring 12 by 5 by 4 cm. The capsule is rather densely adherent to the cortex. On gross section an essentially normal medullary architecture is seen. The entire parenchyma is intensely engorged and deep purple in color. The pelvic mucosa is grossly normal. The extrarenal arteries are patent. In some areas portions of the medullary rays are outlined by interstitial hemorrhage.

Microscopical sections of the kidney have a most striking histologic appearance. The pyramidal portions show extensive necrosis, with hemorrhage extending throughout these zones. There is little evidence of inflammatory exudate surrounding these areas of necrosis. The vessels at the margins are intensely congested. In contrast the cortex appears intact except in one section where a small, fresh infarct is seen. The cortex shows intact glomeruli whose capillaries are engorged. The juxtaglomerular apparatus, particularly the macula densa is unusually prominent in many glomeruli. The convoluted tubules appear small and collapsed, and the epithelial lining is atrophic resembling that seen in the collecting tubules. Frequently, the epithelial cells have a pale, vacuolated cytoplasm. The blood vessels throughout are thin walled. No evidence of local vascular occlusion is seen in the many sections studied.

The histologic changes are those of profound ischemia with infarct-like zones limited almost exclusively to the medulla. The generalized atrophy of the convoluted tubules is undoubtedly secondary to renal ischemia. The apparent prominence of the juxtaglomerular apparatus may be accentuated by the atrophy of the surrounding tubular epithelium which brings out the macula densa especially clearly.

DISCUSSION

It is evident from the foregoing report accurate knowledge of the cause of the proved partial obstruction of the right renal artery is lacking. It is probably justifiable to attribute it to an atheromatous plaque in the aorta at the origin of the renal

artery or in the proximal portion of the renal artery itself.

It was evident that vascular occlusion was present when an anatomically normal kidney with complete loss of function was demonstrated. It was surmised that the obstruction must be incomplete when the blood pressure was found to be rising rather abruptly.

It is interesting to speculate on what would have occurred had the kidney not been removed. The appearance of headache, blurred vision and retinal changes associated with rapidly increasing arterial pressure led me to believe that the entire picture of malignant hypertension would have developed and would have become irreversible as soon as the peripheral arterioles began to show degenerative changes. This belief is strengthened by the experimental observations of Goldblatt¹ and more recently of Selve² of Montreal. Whether the renal cells responsible for the hypertension are in the juxtaglomerular apparatus as Goormaghtigh³ contends or in the descending loop of Henle as Selve² believes is of no importance in this case, since both areas were uninvolved in the necrosis present in the kidney.

A point of some interest for which I do not have an explanation is the appearance of necrosis in the medullary portion of the kidney whereas the cortex remained uninvolved. If the disputed "shunting" vessels of Trueta⁴ actually exist, one would expect the greater damage to be seen in the cortex.

SUMMARY

A case of hypertension due to partial occlusion of the right renal artery with cure of the hypertension by nephrectomy is presented. The case is of unusual interest because it was possible to observe the entire development of the hypertensive syndrome and correlate it with the clinical symptoms produced by the arterial occlusion. A follow-up period of eighteen months revealed no tendency to a recurrence of the hypertension.

45 Jefferson Street

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*Reported through the courtesy of Dr. Robert Tennant, Department of Pathology, Hartford Hospital.

HYPERTENSION DUE TO PARTIAL RENOVASCULAR OCCLUSION

Report of a Case

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IN 1934 Goldblatt¹ aroused much interest by the publication of the results of his experimental production of hypertension in dogs by ingeniously reducing the blood flow through one or both renal arteries. Other investigators have abundantly confirmed his findings.

Within a short time of the appearance of this paper clinical case reports of hypertension in human beings, apparently caused by similar circumstances, began to appear in the literature. It became apparent that severe hypertension from such causes was a very real, but nonetheless a relatively rare, entity. Large series of cases of hypertension have been subjected to searching urologic study, only a small proportion exhibiting unilateral renal disease of possible etiologic significance. Clinical study of the problem has indicated that arterial hypertension can result from any type of renal disease that produces a marked reduction, but not complete ablation of the blood flow through the kidney.

The case reported below is unusual in that the pathologic process exactly reproduced the conditions of Goldblatt's experiments and that it was possible to follow the clinical course of the disease almost from the onset of the vascular obstruction.

CASE REPORT

M P was a 35-year-old factory worker. Her past medical history included an osteomyelitis of the left tibia at the age of 14 that had required several surgical procedures before final healing had been attained, this condition had caused no trouble for 20 years. In 1942 she had suffered a bilateral uveitis, which had responded satisfactorily to the removal of several infected teeth and fever induced by intravenous injection of typhoid vaccine. At that time a careful examination of the retinas by a competent ophthalmologist was recorded as showing no retinal abnormalities. The blood pressure was noted to be 132/88. From 1942 until the onset of the illness under discussion she had been entirely well except for several minor ailments for which she consulted her family physician. On three of these occasions he had recorded her blood pressure at 130/80.

On November 4, 1947, at 7 a m, she experienced a sudden severe, cramping pain in the right upper abdomen. Within the next few hours the pain became dull and moved to the midportion of the abdomen lateral to the umbilicus on the right side. She became nauseated and vomited twice. By mid-afternoon she became so uncomfortable that she was forced to leave work and go home. By this time the pain centered in the right costovertebral angle and the right flank, where it remained the rest of the day and all that night. She ate no supper, vomited bile several times during the night and was unable to sleep. On the following morning she called her doctor, who advised hospitalization for study with a tentative diagnosis of acute retrocecal appendicitis.

On admission to the hospital she still had some pain but it was much less severe and entirely in the right costovertebral

angle. She appeared somewhat pale, but otherwise seemed healthy. The head and neck were unremarkable. A few crackling rales were audible at the base of the right lung posteriorly. The heart was of normal size, the rhythm was regular, and no murmurs were heard. There was slight resistance to palpation in the right upper quadrant of the abdomen, and slight tenderness was elicited in the right costovertebral angle. Rectal examination was negative. The introitus was virginal. The extremities were normal, and the deep and superficial reflexes were physiologic.

The temperature was 100°F by mouth, the pulse 60, and the respirations 18. The blood pressure was 110/70.

Examination of the blood showed a white-cell count of 12,850, with 91 per cent neutrophils. The hematocrit was 40 per cent. The urine was acid, had a specific gravity of 1.015 and gave a + test for albumin but contained no sugar, only rare white blood cells were noted in the sediment.

After admission all the symptoms rapidly disappeared. The elevated white-cell count, with a marked shift to the left, tended toward normal. Except for the initial temperature of 100°F the patient remained afebrile. On the 3rd hospital day an intravenous pyelogram showed a normal left upper urinary tract, but no excretion of the Diodrast was noted on the right side in any of the films.

On the 5th day after admission cystoscopy and retrograde pyelography were done. The bladder and urethra were normal. Both ureteral orifices were in their normal location and appeared normal. Urine was seen to emerge from the left orifice in normal peristaltic spurts, but none was seen to issue from the right side. Catheters were passed easily to each kidney pelvis. Indigo carmine injected intravenously appeared promptly in strong concentration from the left side, but there was no drainage whatever from the right catheter although irrigation with sterile water was easily accomplished with no evidence of obstruction of the catheter. Films were made before and after the catheters had been injected with an opaque medium. No calcific shadows were visible in the renal, ureteral or bladder areas. The tips of both catheters were apparently well placed in the renal pelves. The renal parenchymal shadows on each side were equal and normal. The kidney pelves, calyces and ureters were well filled with contrast material and appeared entirely normal.

On the strength of these findings it was believed that the patient had suffered an obstruction to blood flow through the right kidney of undetermined cause. The blood pressure was rechecked on the following day and found to be 160/90 in contrast to the 110/70 recorded on admission to the hospital a week before. Thereafter, daily blood-pressure readings were taken — all by the same observer and all at approximately the same time of day. A steady rise of both systolic and diastolic readings was noted until, on the 13th day after the onset of the illness, a blood pressure of 180/110 was recorded. On the preceding day the patient had complained of throbbing headache and blurring of vision. An ophthalmologist noted moderate straightening and narrowing of the retinal arterioles and early arteriovenous nicking.

At this time the basal metabolic rate was + 6 per cent, and the blood cholesterol 258 mg and the nonprotein nitrogen 27 mg per 100 cc, the blood sedimentation rate was 13 mm in 1 hour, and the white-cell count was 11,300, with 82 per cent neutrophils, the phenolsulfonphthalein test showed 45 per cent excretion of the dye in 1 hour. The prothrombin time was 100 per cent of normal, and a chest x-ray examination was negative.

The right ureter had been catheterized a second time 3 days after the first cystoscopic examination, and the original findings confirmed. On the 14th day after the onset of the illness the right kidney was exposed through a flank incision. The organ appeared pale and a little bluer than usual. It

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trophe Two of these (Case 21 and 31) had not had any roentgenologic studies at the time of the fire.

Films during inspiration and expiration as well as lateral films were obtained. Fluoroscopy was performed whenever it was thought to be indicated. The observation concentrated on the presence or absence of scars, areas of atelectasis, emphysema.

TABLE 2 *Vital-Capacity Data*

Case No.	SEX	VITAL CAPACITY*		%
		FIRST DETERMINATION	PRESENT DETERMINATION	
		Cc	Cc	
1	M	108	117	2
2	F	48	91	2
4	F	83	89	2
6	F	25	98	2
11	M	No determined	No determined	
15	F	20	82	2
21	M	31	8	2
25	F	No determined	10	2
26	F	No determined	9	2
27	M	56	120	2
31	F	No determined	85	2
32	F	No determined	85	2
33	F	No determined (Tracheostomy)	111	6
34	M	58	114	2
35	M	44	11	4
36	F	64	84	6

*Percentages of values theoretically regarded as normal.

and the position of the diaphragm in inspiration and expiration.

Of the 16 cases, 13 showed no variations from normal in any respect. Two of the remaining cases (Case 4 and 13) showed each a single vertical line in the lower-lung field, representing either a linear scar or a very thin area of plate-like atelectasis. One patient (Case 4) had had seven roentgenologic examinations between the second day and the seventh week of the fire, none of the examinations had shown any abnormality. It is unlikely that the present minimal variation from normal is connected with the disaster. Clinically, the patient is perfectly well. The patient in Case 13, in contrast, had had evidence of atelectasis when seen seventeen weeks after the fire. A third case (Case 21) showed a few similar lines in a basal segment of the right lower lobe. This patient had had no roentgenologic examination at the time of the fire. She had had a virus pneumonia in the spring of 1943. She showed at the time of examination no clinical evidence of disease. The only residual abnormal findings then that might conceivably be attributed to the disaster are the minimal areas of scarring or atelectasis present in Case 13 and 21. Both patients are symptom free.

At the end of the original observation period six years ago, only 2 cases showed residual roentgenologic changes (Case 13 and 19). Case 13 still shows a linear scar or area of atelectasis. We were not able to trace the patient in Case 19, who when

last seen eighteen weeks after the fire still had evidence of air trapping.

DISCUSSION

Analysis of Abnormal or Questionable Findings

Two patients (Case 9, a twenty-seven-year-old woman and Case 14, a thirty-four-year-old man) report occasional dyspnea on effort. The former raises fairly large quantities of thick mucus in the morning, and the latter also raises mucus at the same time. A twenty-nine-year-old man (Case 11) raises a little white or yellow sputum in the morning; he smokes about a package of cigarettes a day. These two complaints are not uncommon in unselected groups of the general population in this climate. The one person (Case 21, a thirty-one-year-old woman) who reports a chronically sore throat dates it from her second delivery in 1946. This is the patient discussed under the section on roentgenology who had a virus pneumonia in 1943.

Vital-capacity estimations show variations from 85 to 117 per cent of the theoretical normal. By this method (McKesson and Scott) 85 per cent of theoretical normal is considered within normal limits, 5 of our patients fell just below the accepted normal level.

Status of Cases Described in Detail in First Report

In our original report we described certain case records as illustrating the characteristics of the different degrees of severity of lung complications.

CASE 16 was used to illustrate Group 2 (rales and emphysema). This man later served overseas as a war correspondent. He is clinically well. His vital capacity, which was 58 per cent of theoretical normal soon after the fire, is now 114 per cent.

CASE 6 was used to illustrate Group 3 of lung complications (rales, emphysema and persistent atelectasis attributed to edema of the air passage). She is now 20, a student in college. She is clinically well. Her vital capacity, which was initially reduced to 25 per cent, is now 98 per cent of theoretical normal.

CASE 20, which we described to illustrate Group 4, has since died, presumably from carcinoma of the breast. Unfortunately, she died outside the hospital so that there was no opportunity to examine the lungs anatomically.

CASE 13. This patient is now clinically well so far as her lungs are concerned and is about to be married. She has some degree of nasal obstruction after plastic operations to her burned nose. Her initial vital capacity was 29 per cent, it is now 82 per cent.

CONCLUSION

From the data on the 16 patients whom we have recently examined clinically and roentgenologically and the 3 additional patients reporting by mail, persistent cough is not reported by any patient and only 3 of the 19 raise any sputum. It seems probable that there is no persisting or secondary pulmonary disease resulting from the fire damage.

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PULMONARY EFFECTS OF THE COCOANUT GROVE FIRE

A Five-Year Follow-Up Study

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THE Coconut Grove fire took place on November 28, 1942. In a previous report¹ we described the initial pulmonary complications in the group of 39 patients admitted to the Massachusetts General Hospital. Finland² has already published the follow-up findings in his series of 92 patients discharged from the Boston City Hospital. He found that symptoms of respiratory disease at four, nine and twenty-six months after the fire were neither frequent nor severe. Persistent cough was the most common symptom at each time period. An occasional patient later began to raise copious amounts of mucopurulent sputum (12 of the 38 patients reporting at twenty-six months). This he regarded as suggesting the development of bronchiectasis.

This study concerns the status of the Massachusetts General Hospital patients five or more years after the fire. The interval seemed sufficient to have permitted the development of any late pulmonary complications that were going to occur.

PLAN OF STUDY

We have written to 29 of the 32 patients discharged from the Massachusetts General Hospital. The other 3 were service men who remained in the hospital only until transfer to Army or Navy installations was arranged. We had no permanent addresses for these 3 patients. We know that 2 of them were returned to full duty by December 12, 1942.

The study was based on questionnaire, physical examination, vital-capacity estimation and roentgenographic examination.

RESULTS OF STUDY

Sixteen patients returned for examination, 6 reports were received by mail, and 7 persons could not be traced. Three of the 6 mailed reports included completed questionnaires (Case 9, 10 and 14). Two patients had died (Case 15 and 20). One is apparently psychotic (Case 35).

Of the 3 patients from whom we have current information but whom we have not seen, 1 is well and 2 have slight dyspnea on exertion. Answers to their questionnaires are indicated in Table 1.

CASE 9 The patient has occasional dyspnea on effort and raises fairly large quantities of thick mucus in the mornings. This case was classified as Grade I severity of lung

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complications, and the patient was discharged a few hours after the fire without having chest x-ray films taken.

CASE 10 The patient, a physician, reports himself as well except for occasional asthma, which he had before the fire.

CASE 14 The patient reports that he has some shortness of breath on walking uphill and that he has some wheeze. He has no other symptoms referable to the respiratory tract.

TABLE 1 Replies to Questionnaire (19 Cases)

QUESTION No	QUESTION	YES	NO
1	Have you any chronic cough?		16+3*
2	Are you short of breath?	2*	16+1*
	If so, do you notice it at rest?		16+3*
	Do you notice it when walking on the level?		16+3*
	Do you notice it when walking uphill?	2*	16+1*
3	Have you any wheeze?	1*	16+2*
4	Are you hoarse?		16+3*
5	Do you raise any sputum?	1+2*	15+1*
6	Do you ever spit blood?		16+3*
7	Do you have pain in your chest?		16+3*
8	Do you have discharge from your nose?	2	14+3*
9	Do you have a chronically sore throat?	1	15+3*

*Replicas so designated refer to patients answering by mail and not interviewed.

Immediately after the fire he had a transient inspiratory wheeze over the front of the left side of the chest and in the left axilla. There was never any abnormal finding in his x-ray film, and examination of his chest was negative at the time of discharge from the hospital on December 10.

CASE 15 This patient committed suicide on January 9, 1943, by jumping through a window.

CASE 20 This patient died on February 3, 1945. In December, 1943, she was operated on for an adenocarcinoma (Grade III) of the left breast, with axillary metastases, in the Baker Memorial Hospital. X-ray films of the lungs were clear at that time.

CASE 35 The patient is reported as being a "psychologic case." She "will not permit a doctor to see her."

PHYSICAL EXAMINATION

Of the 16 patients who have been examined 15 are clinically well so far as their lungs are concerned. One patient (Case 16), a man now sixty-three years old, is symptom free, on examination there were persistent rales in the right axilla.

The results of vital-capacity determination are shown in Table 2.

ROENTGENOLOGICAL FINDINGS†

Sixteen of the original group of survivors had roentgenologic examinations for this follow-up study, varying from five to six years after the catas-

†We are indebted to Dr. Stanley Wyman, of the Massachusetts General Hospital, for the performance of a number of the roentgenologic examinations.

MEDICAL PROGRESS

VITAMIN SUPPLEMENTATION IN HEALTH AND DISEASE (Continued)*

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NUTRITIONAL SURVEYS AND SUBCLINICAL VITAMIN DEFICIENCY

With the exception of one report,⁶⁵ nutritionists in general note that frank deficiency diseases especially vitamin-deficiency diseases, have almost disappeared during the last decade in the United States.^{12, 7, 74} The majority of cases of clinical vitamin deficiency now seen are in association with chronic alcoholism or some debilitating disease,⁷² and a moderate number of cases of scurvy occur in infants because mothers boil the orange juice or cater to dietary dislikes.⁷⁵ The cause of this reduced incidence of gross vitamin deficiency in the United States is unexplained. Blankenhorn⁷² observes that deficiency began to disappear before the enrichment of flour was practiced generally and has continued to wane in spite of the high cost of food, indicating that improvement is probably not due to gain in economic status.

On the other hand, a survey of the many studies of the nutritional state of prisoners of war and of the populations of occupied countries during World War II showed that vitamin deficiency becomes prevalent under adverse conditions. Only a few of these reports are reviewed here. Cartwright and Wintrobe⁷⁶ elicited a history of pellagra in 50 to 70 per cent, wet beriberi in 77 per cent and dry beriberi in 50 per cent of war prisoners from the Philippines and from Japan. Similar findings in the Pacific Theater were reported by others.^{77, 78} In general, the deficiencies were multiple, but two other outstanding symptoms attributed to inadequacy of components of the vitamin B complex were the "burning-feet" syndrome and retrobulbar neuritis.^{24, 49, 79, 82} The syndrome of "burning feet" at night was observed previously in the Spanish Civil War.⁸³ The important information about these two newer syndromes of vitamin deficiency is their failure to respond to crystalline thiamine or nicotinic acid supplements alone, but they improve after ingestion of brewers' yeast or a luxurious diet.^{74, 49, 80, 83} It was mentioned above that the "burning-feet" syndrome might be due to pantothenic acid deficiency.⁴⁹

In contrast with these reports from the Pacific area, the results of nutritional surveys among

European civilians and prisoners of war showed a minimum of vitamin-deficiency signs, although they were very much undernourished with respect to calories.⁸¹⁻⁸⁷ The difference between the European and Pacific types of starvation is probably due to the fact that the diet in the Pacific Theater was primarily carbohydrate, secondary diseases such as dysentery adding to the burden of maintaining adequate vitamin intake. In Europe, however, the dietary intake was generally restricted but more nearly balanced with almost adequate protein and borderline vitamin intake. It should be noted that the vitamin requirements were somewhat reduced by the decrease in metabolic rate that occurs in semistarvation.^{85, 87}

To return to the problem of vitamin deficiency in the United States, in addition to the reports of the rarity of clinical vitamin deficiency today, the proponents of widespread avitaminosis have been dealt a further blow through recent critical surveys, which have demonstrated that many of the so-called specific signs of vitamin deficiency are not caused by a lack of vitamins but by other factors, which are often nonnutritional. The thickening of bulbar conjunctivas, which was formerly attributed to vitamin A deficiency, remained unchanged after two years of therapy with 50,000 I.U. of vitamin A per day.¹³ Similar, but not quite as definitely negative, results of therapy were obtained by Borsook et al.⁸⁸ Darby and Milam⁷⁴ found no correlation between the skin lesions supposedly caused by vitamin A deficiency and low plasma vitamin A levels or a low daily intake of vitamin A. Others have stated that keratosis pilaris is more often due to a deficiency of soap and water than to a lack of vitamin A.^{89, 90} These facts are strong evidence that the so-called signs of vitamin A deficiency are not specific.

Abnormal reflexes, calf-muscle tenderness, plantar dysesthesia and loss of vibratory sense have been considered specific signs of inadequate thiamine intake. Borsook et al.⁸⁸ failed to observe any therapeutic effect of large doses of thiamine, administered over a long period to a group of young aircraft workers, some of whom manifested these symptoms. Likewise, Darby and Milam⁷⁴ found no relation between a low level of thiamine intake and abnormalities of vibration sense, which were found in adults only. These observations suggest both that the specificity of such symptoms of athi-

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ODDITY OF PREGNANCY

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CURIOUS alterations of appetite of the most bizarre nature occur in some pregnant women

CASE REPORT

A well developed and well nourished 39-year-old woman came to the office in her 37th week of pregnancy. She had had eight normal pregnancies, and 7 of the children were living and well. The heart and lungs were essentially normal. The blood pressure was 120/80. There was a vertex presentation, in the left occipitoanterior position, and the fetal heart tones were normal. The teeth were in poor condition, gray and completely eroded or abraded (Fig 1). These flat, table-shaped teeth led to further questioning, which brought to light her strange diet. When she was about 16 weeks pregnant, she suddenly experienced an urge to eat coal. Since her home was heated with oil, she made her husband purchase a 100-pound bag of pea coal. She chewed and ate two or three pieces of coal daily, carefully washing it with water before eating it. She continued to indulge in this strange diet, chewing the coal until the 37th week, when her teeth became eroded and soft and when she began to break up the lumps into small pieces before eating.

She was never constipated and stated that she saw the small pieces of coal in her feces after each bowel movement. She took a normal diet otherwise, and had had no desire to eat coal or any other special foods during her previous pregnancies. She had had no medical or prenatal care previous to being seen by one of us (L. L.) during the 37th week of pregnancy.

She was given dicalcium phosphate with vitamin D, 2 tablets four times daily, and told to refrain from continuing her coal diet. The calcium seemed to satisfy her, and she stopped eating coal. Three weeks later she delivered a normal female infant in the hospital. She had an uneventful puerperium, and now requires extensive dental care.

SUMMARY

A case of a craving for coal, which developed during pregnancy, is presented. This craving was relieved by a prescription of dicalcium phosphate. Permanent damage to the teeth resulted from the coal diet. So far as is known, no similar cases have been reported.



FIGURE 1 Photograph of the Patient's Teeth, Showing the Abraded Lower Central Incisors

The following case concerns a pregnant woman with an insatiable desire to eat coal.

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MEDICAL PROGRESS

VITAMIN SUPPLEMENTATION IN HEALTH AND DISEASE (Continued)*

PERRY J. CULVER, M.D.†

BOSTON

NUTRITIONAL SURVEYS AND SUBCLINICAL VITAMIN DEFICIENCY

With the exception of one report,⁶⁵ nutritionists in general note that frank deficiency diseases especially vitamin-deficiency diseases have almost disappeared during the last decade in the United States.^{14, 72, 74} The majority of cases of clinical vitamin deficiency now seen are in association with chronic alcoholism or some debilitating disease,⁷² and a moderate number of cases of scurvy occur in infants because mothers boil the orange juice or cater to dietary dislikes.⁷⁵ The cause of this reduced incidence of gross vitamin deficiency in the United States is unexplained. Blankenhorn⁷² observes that deficiency began to disappear before the enrichment of flour was practiced generally and has continued to wane in spite of the high cost of food, indicating that improvement is probably not due to gain in economic status.

On the other hand, a survey of the many studies of the nutritional state of prisoners of war and of the populations of occupied countries during World War II showed that vitamin deficiency becomes prevalent under adverse conditions. Only a few of these reports are reviewed here. Cartwright and Wintrobe⁶ elicited a history of pellagra in 50 to 70 per cent, wet beriberi in 77 per cent and dry beriberi in 50 per cent of war prisoners from the Philippines and from Japan. Similar findings in the Pacific Theater were reported by others.^{77, 78} In general, the deficiencies were multiple, but two other outstanding symptoms attributed to inadequacy of components of the vitamin B complex were the "burning-feet" syndrome and retrobulbar neuritis.^{24, 49, 79, 82} The syndrome of "burning feet" at night was observed previously in the Spanish Civil War.⁸³ The important information about these two newer syndromes of vitamin deficiency is their failure to respond to crystalline thiamine or nicotinic acid supplements alone, but they improve after ingestion of brewers' yeast or a luxurious diet.^{4, 49, 80, 83} It was mentioned above that the "burning-feet" syndrome might be due to pantothenic acid deficiency.⁴⁹

In contrast with these reports from the Pacific area, the results of nutritional surveys among

European civilians and prisoners of war showed a minimum of vitamin-deficiency signs, although they were very much undernourished with respect to calories.^{54, 57} The difference between the European and Pacific types of starvation is probably due to the fact that the diet in the Pacific Theater was primarily carbohydrate, secondary diseases such as dysentery adding to the burden of maintaining adequate vitamin intake. In Europe, however, the dietary intake was generally restricted but more nearly balanced with almost adequate protein and borderline vitamin intake. It should be noted that the vitamin requirements were somewhat reduced by the decrease in metabolic rate that occurs in semistarvation.^{85, 87}

To return to the problem of vitamin deficiency in the United States, in addition to the reports of the rarity of clinical vitamin deficiency today, the proponents of widespread avitaminosis have been dealt a further blow through recent critical surveys, which have demonstrated that many of the so-called specific signs of vitamin deficiency are not caused by a lack of vitamins but by other factors, which are often nonnutritional. The thickening of bulbar conjunctivas, which was formerly attributed to vitamin A deficiency, remained unchanged after two years of therapy with 50,000 I U of vitamin A per day.¹³ Similar, but not quite as definitely negative, results of therapy were obtained by Borsook et al.⁸⁸ Darby and Milam⁷⁴ found no correlation between the skin lesions supposedly caused by vitamin A deficiency and low plasma vitamin A levels or a low daily intake of vitamin A. Others have stated that keratosis pilaris is more often due to a deficiency of soap and water than to a lack of vitamin A.^{89, 90} These facts are strong evidence that the so-called signs of vitamin A deficiency are not specific.

Abnormal reflexes, calf-muscle tenderness, plantar dysesthesia and loss of vibratory sense have been considered specific signs of inadequate thiamine intake. Borsook et al.⁸⁸ failed to observe any therapeutic effect of large doses of thiamine, administered over a long period to a group of young aircraft workers, some of whom manifested these symptoms. Likewise, Darby and Milam⁷⁴ found no relation between a low level of thiamine intake and abnormalities of vibration sense, which were found in adults only. These observations suggest both that the specificity of such symptoms of athi-

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ODDITY OF PREGNANCY

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CURIOUS alterations of appetite of the most bizarre nature occur in some pregnant women



FIGURE 1 Photograph of the Patient's Teeth, Showing the Abraded Lower Central Incisors

The following case concerns a pregnant woman with an insatiable desire to eat coal

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CASE REPORT

A well developed and well nourished 39-year-old woman came to the office in her 37th week of pregnancy. She had had eight normal pregnancies, and 7 of the children were living and well. The heart and lungs were essentially normal. The blood pressure was 120/80. There was a vertex presentation, in the left occipitoanterior position, and the fetal heart tones were normal. The teeth were in poor condition, gray and completely eroded or abraded (Fig 1). These flat, table-shaped teeth led to further questioning, which brought to light her strange diet. When she was about 16 weeks pregnant, she suddenly experienced an urge to eat coal. Since her home was heated with oil, she made her husband purchase a 100-pound bag of pea coal. She chewed and ate two or three pieces of coal daily, carefully washing it with water before eating it. She continued to indulge in this strange diet, chewing the coal until the 37th week, when her teeth became eroded and soft and when she began to break up the lumps into small pieces before eating.

She was never constipated and stated that she saw the small pieces of coal in her feces after each bowel movement. She took a normal diet otherwise, and had had no desire to eat coal or any other special foods during her previous pregnancies. She had had no medical or prenatal care previous to being seen by one of us (L. L.) during the 37th week of pregnancy.

She was given dicalcium phosphate with vitamin D, 2 tablets four times daily, and told to refrain from continuing her coal diet. The calcium seemed to satisfy her, and she stopped eating coal. Three weeks later she delivered a normal female infant in the hospital. She had an uneventful puerperium, and now requires extensive dental care.

SUMMARY

A case of a craving for coal, which developed during pregnancy, is presented. This craving was relieved by a prescription of dicalcium phosphate. Permanent damage to the teeth resulted from the coal diet. So far as is known, no similar cases have been reported.

MEDICAL PROGRESS

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aminosis is untrue and that the concept of thiamine-deficiency incidence based upon these signs should be revised downward

The signs most often associated with riboflavin deficiency — namely, corneal vascularization, angular fissures and changes in the buccal mucosa and tongue — have been found without relation to a low intake of riboflavin⁷⁴⁻⁹¹ The corneal vascularization may just as often be associated with physical trauma such as sun, wind or dust,⁹² whereas Darby⁹³ states that at the Vanderbilt Hospital Nutrition Clinic stomatitis due to iron deficiency is seen more frequently than cheilosis and glossitis caused by lack of riboflavin or niacin

Another example of nonspecificity of a supposedly characteristic sign of vitamin inadequacy — in this case, vitamin C — is gingivitis or swelling and blueness of the gums There are several reports of gingivitis in 50 per cent or more of adults examined, but the gingivitis is associated with poor oral hygiene rather than with low plasma ascorbic acid levels⁷⁴ and does not decrease after administration of 100 to 200 mg of vitamin C for three months or longer⁹⁴⁻⁹⁵ Although oral hygiene plays a major role in prevention of gingivitis, vitamin C may contribute, as shown in a well controlled study by Linghorne et al⁹⁶ They found that ascorbic acid therapy alone would not improve gingivitis but that, once local therapy had alleviated involvement of the gums, daily intakes of more than 22 mg of vitamin C would deter the recurrence of gingivitis

Inasmuch as many estimates of the incidence of vitamin deficiency in the United States have been based upon the presence of signs that are now shown to be nonspecific, I believe that the problem of vitamin deficiency is minimal Therefore, it becomes apparent that, with few exceptions, food intake supplies the minimal requirement of essential vitamins, and the widespread use of vitamin supplements does not seem indicated for treatment of an almost nonexistent vitamin-deficiency state

There still remains the possibility that vitamins in addition to those in the general diet are of value for improving health or well-being and for promoting recovery from disease Information obtained from review of the following studies of this problem will indicate whether or not the average American diet contains optimal quantities of vitamins

To quote from Keys,⁹⁷ who appreciated the necessity of restricting his interpretation to the small number of studies on vitamin-fitness relations that were acceptable and well controlled, "the great bulk of the evidence indicates no gain in fitness of adults from vitamin supplementation added to a good American diet" There is no improvement in tolerance to hot or cold environments from the use of vitamin supplements and no good evidence that vitamin requirements are increased during

extremes of temperature⁹⁸⁻⁹⁹ Contrary to the statement that "biochemical avitaminosis" has been found to exist in the majority of aged persons,¹⁰⁰ Vernon and McKinlay¹⁰¹ found no beneficial effect over a twelve-month period from vitamin supplementation in senile patients In two well controlled studies involving more than 500 employees of an aircraft plant⁹¹ and 241 steel workers,¹⁰² daily supplements of a multivitamin capsule showed no more beneficial effect on sense of well-being, absenteeism, appetite, sleep and increased output of work than did placebo capsules Comparison with a control group receiving neither placebos nor vitamin capsules leaves no doubt about the psychologic and morale-improving effect of any sort of medication It is the psychologic effect of vitamin supplements that opens to question the many reports of beneficial effects It has already been mentioned that added vitamins failed to alter the biomicroscopic lesions observed among the aircraft workers⁹¹ These two reports have an increased value in an attempt to determine whether there is need for supplementing the average American diet with vitamins because dietary surveys among these workers showed that intakes of vitamins were below the recommended dietary allowances of the National Research Council in a large number of the subjects⁸⁸ As additional evidence, it was found that vitamin supplements had no effect on the growth, strength, nutrition, fatigue potential, incidence or severity of clinical conditions, hearing and absenteeism among 1620 British schoolchildren observed over a one-year period of controlled study¹⁰³ Dietary surveys made in conjunction with this investigation showed that the average vitamin intakes were well below recommended standards and cast doubt upon the validity of the American "recommended dietary allowances"¹⁰³

In another three-year study of 315 workers in trinitrotoluene, multivitamin capsules did not decrease the occurrence of toxic symptoms in the treated group as compared with controls¹⁰⁴ In this study there was an interesting but probably not significant observation of 14 cases of hepatitis among the treated group in contrast to only 2 cases among the controls

In addition to these reports of the general ineffectiveness of vitamin supplements, several investigations show lack of benefit from the administration of specific vitamins in certain pathologic states These findings undermine opinion widely accepted previously that the specific vitamins were indicated in these conditions, 50,000 to 150,000 I U of vitamin A per day did not decrease color blindness¹⁰⁵ or reduce thickening of the bulbar conjunctivas¹⁰⁶ Diabetic neuropathy is not relieved by large doses of thiamine and other components of the vitamin B complex, but only by adequate insulin and diet therapy¹⁰⁵⁻¹⁰⁷ Moreover, diabetic neuropathy has developed in patients who

have been taking excessively large doses of vitamins¹⁰⁶ There was no evidence that large doses of crystalline components of the vitamin B complex had any significant effect upon rate of healing or survival after severe burns³⁶ A study of the effectiveness of various types of therapy in hepatic cirrhosis by means of serial liver biopsies raises doubt whether supplements of vitamin B complex have any beneficial effect beyond that of a high-carbohydrate, high-protein diet alone,¹⁰⁸ and excess quantities of vitamins had no protective effect on liver function as measured by urobilinogen excretion and bromsulfalein clearance during postoperative convalescence¹⁰⁹ Although one investigation showed a slight beneficial effect of added thiamine over placebo tablets in the mental responses of children in an orphanage as measured by results of 15 out of 30 aptitude tests,¹¹⁰ the results are probably not significant Moreover, negative results for improvement in growth, vision and learning after administration of 2-mg supplements of thiamine to 1 of each of 25 pairs of identical twins for nine months were observed in a carefully planned study by Robertson et al¹¹¹ These negative findings are even more impressive when it is noted that 50 per cent of the experimental subjects were eating 20 to 40 per cent less vitamins than the optimal levels of the "Recommended Dietary Allowances"

The conclusion to be drawn from these investigations is that the American diet, even though it may contain a smaller quantity of vitamins than the generous recommendations of the National Research Council suggest, generally supplies optimal amounts of vitamins and that the indiscriminate use of vitamin supplements does not benefit public health or promote recovery from diseases Such a conclusion does not deny the existence of an occasional case of vitamin deficiency that requires short-term vitamin supplementation, nor does it deny that the use of large doses of specific vitamins may not be of benefit in certain diseases in which the vitamin has a pharmacologic rather than a nutritive action Reports of the specific therapeutic uses of vitamins are reviewed below

SPECIFIC THERAPEUTIC USES OF VITAMINS

Reports of the curative or beneficial effect of large doses of a specific vitamin in a given disease are legion, and such reports, along with advertisement of supposed malnutrition, have acted as stimulants to vitamin sales In many cases reports of therapeutic success with a vitamin are the result of uncontrolled clinical investigations that do not consider either the natural history of the disease or the possible psychologic effect of vitamin pills At the risk of omitting many valuable references, only a few investigations can be reviewed

Massive doses of vitamin A have been a therapeutic favorite of dermatologists, 100,000 to 240,000 I U of vitamin A are said to bring about slow

improvement in some cases of Darier's disease^{112 113} Similar doses of vitamin A were believed to cause regression in both seborrheic and senile keratoses in all 50 cases treated for three or four months, whereas 30 control cases remained unchanged¹¹⁴ Thirty-seven per cent of 42 cases of plantar warts were cured by 100,000 I U of vitamin A daily for five weeks to nine months¹¹⁵ Although the results with vitamin A were not nearly as effective as x-ray therapy, the investigators recommend vitamin A treatment because of its safety Massive doses of vitamin A also are reported to improve pityriasis rubra pilaris¹¹⁶ A striking clinical and pathological improvement was shown by 14 of 18 cases of leukoplakia vulvae treated with 250,000 to 500,000 units of vitamin A per day by mouth, in addition to 50,000 units twice a week by injection¹¹⁷ If confirmed, this observation has considerable significance in view of the difficulties associated with the treatment of leukoplakia vulvae

I agree with many conservative dermatologists who are skeptical about reports of therapeutic benefits from vitamin A Consequently, negative reports from well controlled investigations are important for keeping therapeutic enthusiasm in balance Such a report is that of Lynch and Cook,¹¹⁸ who found that vitamin A had no special beneficial effects in the treatment of acne vulgaris

In 2 cases reported by Simkins,¹¹⁹ "cures" of thyrotoxicosis were effected by the administration of 200,000 to 400,000 I U of vitamin A per day for a year Most clinicians have discounted earlier reports of the effectiveness of vitamin A therapy in hyperthyroidism, but there has been enough suggestive evidence that vitamin A may depress thyroid function to warrant a complete investigation of this problem

The intravenous use of large doses of crystalline components of the vitamin B complex as an agent for determining arm to tongue circulation time has been reported by Swenson¹²⁰ Although it is not exactly a pharmacologic use of B vitamins, the safety of this method merits consideration Massive doses of thiamine to decrease the possibility of arsenic toxicity are suggested by Sexton and Gowdey,¹²¹ but as yet this use for thiamine has not had much of a clinical trial Mention is made of the beneficial effect of very large doses of nicotinamide for all pruriginous states,¹²² and of 25 to 300 mg of nicotinic acid for chilblains¹²³

There has been considerable enthusiasm for the use of pyridoxine in the treatment of radiation sickness during the last five years Representative reports^{124 125} stress the good results in 60 to 65 per cent of cases treated with oral or intravenous doses of 100 to 400 mg per day In view of the constantly changing fashions in the treatment of radiation sickness and of the favorable effects formerly attributed to the use of other components of the vitamin B complex, I believe that there should be

some reservation in accepting pyridoxine as the specific for radiation sickness

Lewy and Fox¹²⁶ report success in the treatment of cases of resistant Ménière's syndrome and of vertigo of undetermined origin with 100 mg of pyridoxine per day. Intravenous injections of 200 mg were said to have a remarkable effect on raising the white-cell counts of patients who had been made agranulocytic by thiouracil,¹²⁷ but pyridoxine was ineffective in the granulocytopenia of chronic benzene poisoning.¹²⁸ The possibility of spontaneous remissions must be considered when the effect of pyridoxine on the granulocytopenia due to thiouracil is evaluated. Other negative reports of value are the failure of pyridoxine in the treatment of epilepsy¹²⁹ and in the treatment of nausea and vomiting of pregnancy.¹³⁰

Promise of benefit from the use of daily doses of 400 mg of calcium pantothenate in 14 cases of discoid lupus erythematosus is reported by Goldman,¹³¹ who is aware of the capriciousness of response of this disease to therapy.

To judge from numerous reports of success, para-aminobenzoic acid seems well established as a specific therapeutic agent in the rickettsial diseases. Flinn et al¹³² compared 10 patients with Rocky Mountain spotted fever who received para-aminobenzoic acid with 13 untreated patients who recovered from the disease. As a result of the drug, the average duration of fever was reduced from seventeen and a half days to ten and a half days, and the treated patients made a more rapid clinical recovery.¹³² Ravenel¹³³ recommended dosages of 0.5 to 1.0 gm per pound of body weight per day. Because the kidneys excrete para-aminobenzoic acid rapidly, oral administration every two hours is necessary to maintain therapeutic blood levels of 30 to 60 mg per 100 cc.¹³² The drug is buffered in 10 cc of chilled 5 per cent sodium bicarbonate solution to decrease nausea and acidosis.¹³³ Administration should be continued for several days after the patient has become afebrile.¹³³ Greeley¹³⁴ suggests using pressed tablets of the sodium salt of para-aminobenzoic acid for slower absorption. If parenteral therapy is necessary, a 25 per cent solution of the sodium salt adjusted to pH 7 may be given by continuous intramuscular or intravenous drip.¹³⁴ Since the drug does not kill rickettsias but inhibits their growth, it is most effective early in the disease.¹³⁵ Para-aminobenzoic acid has also been effective in scrub typhus¹³⁶ and murine typhus.¹³⁷

Further therapeutic possibilities of para-aminobenzoic acid have been enthusiastically but critically described by Zarafonitis.¹³⁸ On the assumption that large doses of the drug might inhibit neoplastic cells with disordered metabolic function, daily doses of 48 gm of the drug were given to patients with leukemia.¹³⁸ A marked drop in white-cell count took place, but there was no essential change in

the clinical condition of the patients.^{138, 139} There is not sufficient space to discuss the rationale for therapy in each type of disease but para-aminobenzoic acid in doses of 15 to 24 gm per day was found to be beneficial in lymphoblastoma cutis, lupus erythematosus, dermatomyositis, scleroderma and sulfonamide-resistant dermatitis herpetiformis.¹³⁸

Another effect of para-aminobenzoic acid that may be of value clinically is its power to cause a great increase in the blood salicylate level when both drugs are given together.¹⁴⁰ The mechanism of this effect has been shown to be reduced detoxication and decreased urinary excretion of salicylates.¹⁴¹ Para-aminobenzoic acid may also reduce the metabolic rate of the body. In an unconfirmed report, Berman¹⁴² stated that daily intravenous doses of 1.0 to 1.5 gm of the sodium salt of para-aminobenzoic acid for three to nine months resulted in a permanent fall of the basal metabolic rate and clinical improvement in all 6 cases of thyrotoxicosis in which this therapy was used.

Several pharmacologic uses for vitamin C have been mentioned, but none of these have confirmation or stem from well controlled studies. Most promising of the group is the report that vitamin C in doses of 500 to 1000 mg per day caused a great reduction of methemoglobinemia in 2 cases.¹⁴³ Chapman and Shaffer¹⁴⁴ found that 250 mg of ascorbic acid increased the minimum lethal dose of Mercurhydrin for dogs by 50 per cent and suggest that 500 mg of vitamin C be mixed with 2 cc of Mercurhydrin in the treatment of congestive failure. Although Klasson¹⁴⁵ reports that 150 to 600 mg of vitamin C per day seemed to decrease the severity of poison-oak dermatitis and prevented the development of dermatitis in 23 out of 24 poison-oak-sensitive persons after exposure, most dermatologists have been disappointed with the use of ascorbic acid in the therapy of poison-ivy dermatitis. Finally, Charpy¹⁴⁶ has the clinical impression that a daily dose of 100 mg of vitamin C eliminated heat prostration in a group of 31 men working at temperatures of 100 to 120°F, but this observation is not in keeping with carefully controlled studies, which showed no increase in resistance to hot environments from the use of large amounts of vitamin C and other water-soluble vitamins.⁹⁸

The cure of lupus vulgaris (tuberculosis of the skin) by massive doses of vitamin D, averaging 100,000 to 150,000 units per day for three months or longer, was first reported by Charpy¹⁴⁶ and Dowing¹⁴⁷ and was subsequently confirmed by numerous other investigations. The only adverse report is that of Ingram and Anning,¹⁴⁸ who observed cures in only 4 patients and improvement in 23 others out of 158 cases treated with massive doses of calciferol. There is no explanation for this divergence of results. In general, 60 to 75 per cent cure can be expected from this type of treatment.¹⁴⁹

Charpy¹⁴⁶ believes that oral administration of the drug is superior to parenteral and that an alcoholic solution of vitamin D is more satisfactory than the oil solution but others found that the route of administration and the type of vehicle for solution of the vitamin D made little difference in the results of therapy. Doses of 150,000 units per day were usually more effective than 100,000-unit doses, and an ineffective dose remained ineffective no matter how long it was continued.¹⁴⁷ There has been no correlation between clinical results and serum calcium levels.¹⁵⁰ During the first few weeks of treatment nearly every patient has a Herxheimer-like reaction, with increase in activity of the skin lesions, a more positive tuberculin test and an increase in erythrocyte sedimentation rate.^{150, 151} Local treatment of the lesion at this time is important for good results.¹⁵¹ The greatest clearing of the lesions occurs within four to eight months.¹⁵⁰ but Charpy¹⁴⁶ believes that treatment should be prolonged for a year or two because histologic cure is considerably slower than clinical remission. Toxic symptoms (to be discussed in a later section of this review) from such large doses of vitamin D were noted in 16 to 50 per cent of the cases treated.^{147, 148, 150, 151} but Dowling¹⁵² points out that often clinical improvement is most striking just when the patient is beginning to look and feel ill from the cumulative effect of treatment. Nephritis and arteriosclerosis contraindicate the use of vitamin D. The mode of action of vitamin D in lupus vulgaris has been much debated but is not understood.

The use of massive doses (100,000 to 900,000 units per day) of vitamin D in sarcoidosis has been tried on a limited scale^{153, 154} with improvement or even clearing of the skin lesions but with marked toxic reactions. As a result the benefit to be derived is questionable. Likewise it has been recommended after critical evaluation of the results of therapy that the use of massive doses of vitamin D in rheumatoid arthritis is neither beneficial nor justified.¹⁵⁵

The pharmacologic use of vitamin E has been the subject of much heated controversy largely owing to the numerous enthusiastic reports from Shute and his co-workers. Other investigators have been unable to confirm Shute's observations. Vogelsang, Shute and Shute^{156, 157} claim to have treated 1500 patients with angina, rheumatic heart disease, hypertensive heart disease, congestive failure and other types of heart disease with 200 to 900 mg of vitamin E per day. They state that vitamin E is the most effective known drug in heart disease and that 80 per cent of the patients treated improve to such an extent that they return to activity even after great disability. Vitamin E is said to decrease capillary permeability, produce

capillary dilatation, reduce anoxia of the cardiac muscle, prevent and resolve thrombi and promote vascularization of scar tissue.¹⁵⁷ I do not believe that these actions of vitamin E have been proved, although Shute et al¹⁵⁵ present an almost convincing review of the function of vitamin E based on biochemical and animal studies.

In a carefully controlled study that avoided both subjective impressions of the patients and natural variations in disease, Levy and Boas¹⁵⁸ found that daily doses of 200 to 800 mg of vitamin E given for three to eleven weeks to 13 patients with angina pectoris were completely ineffective. Baer et al¹⁶⁰ investigated the effect of 300 to 400 mg of vitamin E per day for three to six months in 22 patients with various cardiac conditions and likewise observed no unequivocal evidence of improvement. Similar negative results were obtained by Donegan et al¹⁶¹ when they treated 21 cases of cardiovascular disease with vitamin E for five to twenty months. The consensus of medical opinion in the United States is on the side of the negative results from the use of vitamin E in heart disease, and it questions the validity of Shute's observations. On the other hand, the British opinion, as reflected by an editorial¹⁶² that completely reviews all the therapeutic uses of vitamin E, holds that Shute's claims are plausible and that further controlled clinical tests are indicated.

Additional unconfirmed reports state that vitamin E is beneficial in the treatment of nephritis,¹⁶³ toxemias of pregnancy,¹⁶⁴ purpura,¹⁶⁵ the menopausal syndrome,¹⁶⁶ Dupuytren's contracture,⁶⁹ fibrositis,¹⁶⁷ various skin diseases of the degenerative collagenous group¹⁶⁸ and a host of peripheral vascular diseases.¹⁶²

Aside from the treatment of prothrombin deficiency there has been very little pharmacologic use of vitamin K. One report of the beneficial effect of 20 mg twice a day in 8 cases of chilblains was made by Wheatley.¹⁶⁹ No prothrombin levels were obtained and improvement was measured by clinical response. The rationale for using vitamin K in this condition was based upon the assumption that in chilblains there may be increased permeability of the blood vessels and diminished coagulability of the blood. Another possible effect of vitamin K to be briefly noted is the observation that half of 15 cases with chronic essential hypertension had a significant reduction in blood pressure after oral or intravenous administration of Synkavite.¹⁷⁰

In contrast with the lack of indications for wholesale vitamin supplementation on the basis of deficiency disease the pharmacologic uses discussed above constitute a definite need for specific vitamins in certain diseases.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35511

PRESENTATION OF CASE

First admission A sixty-seven-year-old man was admitted to the hospital complaining of three episodes of terminal hematuria within the past two years, the last episode occurring four months prior to admission.

For four months, the patient had noted slightly increased frequency and occasional dribbling, but had no nocturia, pain, or retention. Physical examination at the time of admission was negative. The urine had a specific gravity of 1.022 and gave a + test for albumin, with occasional red and white cells in the sediment. The nonprotein nitrogen was 27 mg per 100 cc. An intravenous pyelogram showed good kidney function bilaterally. The

ureters were normal, but a slight deformity was noted at the base of the bladder.

On cystoscopy a 1.5-cm papillary tumor was seen just above the left ureteral orifice, and there were scattered small tumor implants elsewhere. Colon bacilli were grown from the catheterized urine. The primary tumor and implants were fulgurated and 8 l-millicurie-radon seeds were implanted above the left ureteral orifice. The patient was discharged much improved. The pathological report of the bladder tumor was carcinoma, Grade III.

Second admission (one month later) Three weeks prior to readmission external radiation therapy was begun at another hospital, following which the patient noted frequency and dysuria. For two days before admission he was nauseated and vomited. On the day of admission he had two shaking chills, a temperature of 102°F, right-flank pain and costovertbral-angle tenderness.

Physical examination was unchanged. The urine had a specific gravity of 1.014 and gave a +++ test for albumin, and the sediment was loaded with red cells and pus. *Staphylococcus aureus* was recovered on culture. The nonprotein nitrogen was 34 mg per 100 cc. An intravenous pyelogram showed good kidney function, a smooth bladder outline and some dilatation of the lower end of the left ureter. Following treatment with sulfathiazole the symptoms subsided, and the patient was discharged to continue sulfonamides at home.

Third admission (five years later) After two uneventful years the patient again began to have intermittent hematuria, either primary or total, occurring in widely spaced episodes lasting up to two days. There were also nocturia and slight dysuria. On admission the urine had a specific

gravity of 1.014 and gave a ++ test for albumin, the sediment contained many red and white cells, and yielded *Staph albus* on culture. Three grams of prostatic chips obtained by transurethral resection showed stromal hyperplasia. The bladder outlet was noted to be irregularly contracted at the time of operation, but no recurrence of tumor was seen.

Fourth admission (six weeks later) The patient was then well except for one bout of hematuria. The night before this admission he felt chilly, had left-flank pain, passed liquid and then clotted blood and went into acute retention. On admission the white-cell count was 14,000. The urine had a specific gravity of 1.012, gave a +++ test for albumin, was loaded with pus and yielded *Staph aureus* and *Staph albus* on culture. Intravenous pyelograms showed good function on the right, impaired excretion on the left, and dilatation of the lower left ureter. The patient responded to catheterization and sulfonamide therapy and was discharged improved after twelve days.

Fifth admission (one year later) After about six months there was still another recurrence of episodic hematuria every two or three weeks and the onset of hesitancy and a weak stream. On several occasions, clots in the bladder necessitated catheterization. On this admission the urine had a specific gravity of 1.016, gave a + test for albumin and contained *Staph albus* and many red cells. The temperature was normal, and the white-cell count 10,800. Following spontaneous passage of a large clot the urine cleared, and the patient was discharged.

Sixth admission (three months later) Following discharge there were two short episodes of hematuria. On the day before admission the urine became scanty and grossly bloody, with large clots. On physical examination the bladder was percussed half way to the umbilicus. The urine had a specific gravity of 1.022 and contained much albumin and red cells. Immediately following admission the temperature rose to 101°F and for the next week spiked to between 100 and 102°F daily. The white-cell count was 14,400. Two 500-cc whole-blood transfusions were given following hemoglobin determinations of 10.5 and 9.7 gm. The nonprotein nitrogen of 56 mg per 100 cc on admission rose steadily to a high of 135 mg and then subsided gradually to 84 mg on discharge. Fluoroscopy showed elevation of the left leaf of the diaphragm and some atelectasis of the left lower lobe of the lung. There was also aching left-flank pain. Cystoscopy demonstrated multiple small areas of hemorrhage in the bladder mucosa but no recurrence of the tumor. The right ureteral orifice was crescentic, and the left could not be visualized. The patient was maintained on intravenous feedings, penicillin and streptomycin. The urine

cleared, and output was good. The patient left improved after six weeks of hospitalization.

Final admission (one month later, about seven years since the first admission) The patient was then well for three weeks, when hematuria and passage of clots recurred. On admission the urine had a specific gravity of 1.012 and contained much albumin, red cells, pus and bacteria. The nonprotein nitrogen was 45 mg per 100 cc. The white-cell count was 7000, and the hemoglobin 9.2 gm, and the patient was given 500 cc of whole blood. The intravenous pyelogram showed good function of the right kidney, the cortex of which was noted to be thin. No excretion could be detected on the left.

On the ninth hospital day a bilateral ureterocutaneous anastomosis was done, following which the patient passed moderate amounts of urine from the right kidney and small amounts from the left. The nonprotein nitrogen began to climb, reaching 98 mg per 100 cc. There was onset of diarrhea, guaiac-positive stools were noted. The white-cell count began to rise, and the hemoglobin remained low. On the sixteenth hospital day the patient had a shaking chill and began vomiting. Urinary output declined markedly. Returns from bladder irrigation consisted of foul-smelling, semisolid material.

During the last week of the hospital stay, the temperature spiked to 103°F and then declined to normal. The patient died on the twenty-third hospital day.

DIFFERENTIAL DIAGNOSIS

DR GEORGE G SMITH* This patient's complaint on admission was three episodes of terminal hematuria. I want to speak of the significance of terminal hematuria. With initial hematuria in a man over fifty, within the prostatic age, the chances are that the blood is coming from the prostatic urethra, if it is terminal hematuria, it probably is from the bladder, whereas renal hematuria usually gives total discoloration of the urine.

Nothing is said here about a rectal examination or about the amount of residual urine.

The frequency and dysuria on the second admission might have been due to x-ray treatment if he had had enough to cause congestion of the bladder mucosa. The costovertebral-angle tenderness sounds as if he had an attack of acute pyelonephritis on the right side.

At the third admission we are again kept in the dark about what the prostate felt like and how much residuum the patient had, but it is evident that he had prostatic obstruction since a transurethral resection was performed.

About six years after the tumor of the bladder was treated, the bladder apparently was free of tumor. It would make the diagnosis easier if we

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were told where the blood was coming from and if the patient was cystoscoped

Again, on the fourth admission, we have no information of the cause of the hematuria. Among other things, it might have come from the remnant of the prostate left behind at transurethral resection. It is not unusual to have episodes of hematuria occasionally, even for several years after transurethral resection.

A marked elevation of nonprotein nitrogen points definitely to bilateral renal involvement. At first sight it seems as if the cause of death in this patient would be easy to put one's finger on. I think he died chiefly from pyelonephritis.

He had had one previous attack of infection on the right side and now showed evidence of marked infection, with pain, elevation of the left leaf of the diaphragm and entire destruction of the function of the left kidney. I believe that probably was the result of implantation of the radium near the ureteral orifice. One can postulate swelling of the radium-affected tissue and infection traveling up the lymphatics of the ureter bringing about the combination of infection and obstruction, which led to pyelonephritis with a gradual destruction of the kidney on the affected side. There is nothing in the history to explain obstruction of the lower right ureter, and yet one of the late intravenous pyelograms showed that the right kidney had a thin cortex, this probably was the result of repeated attacks of pyelonephritis.

Let us look at one or two of the intravenous pyelograms.

DR JAMES J MCCORT. An intravenous pyelogram made on the first admission shows the kidneys to be within normal limits in size and shape, both are satisfactorily outlined. After intravenous administration Diodrast was excreted in good concentration within five minutes. The pelvis and calyces are not dilated. The films taken at fifteen minutes confirm this impression, but the film of the bladder at thirty minutes shows a slight irregularity on the left inferior margin of the bladder. A film of the bladder after evacuation again shows this slight irregularity.

DR SMITH. It is rather difficult to explain why the patient was not definitely improved by his skin ureterostomies. I do not know whether he had catheters put up to the kidneys or drainage without catheters, which we sometimes do. We can often clear up or alleviate the effects of marked pyelonephritis by adequate drainage of the kidney pelvis by means of nephrostomy, pyelostomy or ureterostomy. But in this case the drainage did not accomplish this. It makes me think that there was another factor involved besides obstruction of the lower ureter. The pyelonephritis may have been too far advanced to be relieved by drainage alone.

Another thing that ought to be explained is the repeated attacks of hematuria. In fact, this was really the chief item in the past history. At the sixth admission, cystoscopy showed multiple small areas of hemorrhage in the bladder mucosa. Whether the blood came down the left ureter and indicated a carcinoma of the left renal pelvis or ureter, I do not know, but it would explain the bleeding. No tumor was found in the bladder. However, the wall of a bladder that has been chronically inflamed for a long time will sometimes bleed so that one has to do a cystostomy. I remember 2 cases in which it was necessary to do a total cystectomy to stop bleeding.

An item that I think is important is that the tumor was classified as Grade III. That is significant and means that it was an unusually malignant tumor even though it did not recur in a period of seven years. It is perfectly possible, and I think probable, that the lesion extended from the largest tumor here into the bladder wall, which may account for the fact that when the bladder was examined cystoscopically bleeding areas were seen in the bladder mucosa.

The picture that Dr McCort showed us is suggestive of a mass behind the bladder and more or less around the bladder neck. The dilatation of the right kidney, which was due, perhaps, to pyelonephritis, may also have been due to obstruction of the lower end of the ureter by a malignant lesion involving the bladder wall or coming up behind the bladder. The elevation of the left leaf of the diaphragm and the aching pain around the left kidney may indicate perinephritic abscess secondary to the severe left renal infection. I believe that if this man had been cured of his cancer the first time it was treated, as he appeared to be, and even if his left kidney had been destroyed by the effect of radium at the lower end of the ureter or from some other reason, the right kidney would have carried on adequately. But the right kidney evidently was seriously damaged. Later on, after a number of years, if this patient did have carcinoma that extended into the bladder wall and around the base of the bladder, it is more than likely that he had metastases to the aortic lymph nodes, and possibly in the lung—a disseminated carcinomatosis. My impression is that death was primarily due to pyelonephritis, but he probably had extensive carcinoma and certainly obstruction to the lower ureters.

DR FLETCHER H COLBY. This patient is very interesting from certain points of view. It is not quite clear in the protocol that he had a great deal of external radiation. He was one of the early patients given external radiation on the 1200-kilovolt machine at the Huntington Memorial Hospital. In addition he had a large amount of interstitial radiation in the bladder tumor. This man, as I remember, had about 12,000r of external radiation at

the time, or soon after the radium was implanted, so that he was given an unusual dose of both external and internal radiation. I do not think Dr Smith appreciated the fact that he had had so much radiation to his bladder, that might have made a difference in the way he thought about the bleeding.

DR SMITH Yes.

DR COLBY The patient was followed carefully in the seven or eight years after the initial tumor was treated in this way. I may add also that when he was first seen a sufficient amount of induration was felt on bimanual examination so that it was believed that this tumor probably involved the whole thickness of the bladder wall. It was subsequently shown that that was not true. At any rate, the patient was cystoscoped on many occasions following that, and at no time was the slightest evidence of recurrence of the primary bladder neoplasm seen. He had a sufficient amount of difficulty in voiding so that a transurethral resection was done on the prostate. I think the difficulty was due to contraction of the bladder neck rather than real prostatic hypertrophy. At no time did the prostate feel very large, and the bleeding subsequently was definitely not from the area of resection. It was a diffuse bleeding from all over the bladder, and at no time, even when he was actively bleeding, was any blood seen by cystoscope coming from either one of the ureteral orifices. It was again perfectly obvious on clinical examination that this man had progressive fibrosis of the bladder involving both ureteral orifices, more on the left, which had radium planted nearby, than on the right, but both orifices were involved in disease.

DR McCORT Did you specify the tumor dose as 12,000 r?

DR COLBY That was the dose measured in air.

DR McCORT The actual tumor dose was therefore about 6000 or 7000 r.

DR COLBY The external radiation was so extensive that this man was practically incontinent of urine for months.

DR SMITH I think it is worth saying that I have seen some patients who have been treated with extensive radiation, both internal and external, and after some years the ureters became fibrosed into a spindle-shaped canal, which gradually became obstructed. They usually go on all right after that. I suppose that happened to this patient's ureters. I think it would have made a little difference in my consideration of the case if I had realized that he had had more than the conventional dosage of x-ray because that would have explained the ureteral obstruction.

CLINICAL DIAGNOSES

Carcinoma of bladder
Radiation fibrosis of bladder
Uremia

DR SMITH'S DIAGNOSES

Pyelonephritis, bilateral
Obstruction of lower ureters by tumor

ANATOMICAL DIAGNOSES

(Carcinoma of bladder cured by radiation)
Radiation fibrosis of bladder and ureters
Papillary carcinoma, Grade III, left renal pelvis
Pyelonephritis, acute and chronic, bilateral
Pelvic abscess, small

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY At post-mortem examination we found no evidence of metastatic or recurrent tumor in the bladder. The bladder wall was fibrotic. Both ureters were bound in a heavy mass of scarred tissue, and it was very difficult to trace the right one more than about 3 cm from the ureteral orifice. The left ureter ended in an abscess cavity, 3 cm in diameter. The surprise of the autopsy was that a large part of the left kidney was replaced with tumor. It was a papillary carcinoma of the renal pelvis, filling the pelvis and extensively invading the renal tissue. The remainder of that kidney was virtually destroyed by pyelonephritis. The right kidney was free from tumor but showed almost as extensive infection. We could find no evidence that the bladder tumor had extended or recurred, and I believe that this tumor of the renal pelvis was an entirely independent separate tumor.

DR SMITH That did not show in the early intravenous pyelograms.

DR COLBY I do not believe that the tumor of the left kidney was an essential factor in the production of symptoms. The essential feature was the fact that here was a man whose bladder cancer was definitely cured by radiation. But it is the exception, and, not to mince words, the cure was as lethal as his original disease. We had always believed in treating these patients with cancer by external radiation that it was an agent to be used cautiously not with the idea that it would be curative, simply palliative. Although this patient was cured of the cancer, we wonder if the effects of radiation resulted in his death.

CASE 35512

PRESENTATION OF CASE

A sixty-two-year-old man entered the hospital for study.

About six years before admission, the patient began having recurrent attacks of five to ten minutes' duration in which there were involuntary jerking movements on the right, beginning in the face and spreading to the right arm and then to the leg. The patient was unable to speak during the attacks but did not lose consciousness between

attacks he felt entirely well. However, as time went on, the attacks slowly increased in frequency. Two years before admission, he entered a community hospital, where no abnormalities were found on examination. He was discharged on anticonvulsive medication, which he took irregularly. About six months before admission, the patient began to be confused. Two months before admission his wife noticed that he tended to drag the right leg slightly in walking. The seizures meanwhile became progressively more frequent, occurring two or three times a day in the two months before admission. There was no change in the character of these attacks. Throughout the illness, the patient had no headaches and had not felt ill. About a month before admission, he re-entered the same community hospital. His general physical condition was good, and there were no abnormalities on routine physical examination. Neurologic examination disclosed impaired ability to understand commands, recent poor memory and confusion as to the chronology of his life and his illness, although he was oriented as to date and place. He was able to read, write and name objects. The right fundus was normal except for moderate arteriosclerosis, the left fundus could not be seen because of cataract. Visual acuity was normal in the right eye. Confrontation fields were full. The right pupil was slightly larger than the left, both reacted normally to light and on convergence. Ocular movements were normal. There was slight right lower facial weakness on both volitional and emotional movement. The other cranial nerves were intact. There was falling away of the right arm and leg when outstretched, and on walking the right leg moved stiffly and over a smaller range than the left. The tendon reflexes were more active on the right, the plantar reflexes were normal. There were no sensory changes, although the patient was not sufficiently co-operative for refined testing.

X-ray films of the skull were normal. The spinal-fluid pressure was equivalent to 130 mm. of water, with no cells, and the protein was 44 mg. per 100 cc. The Wassermann reaction was negative. An electroencephalogram showed a "definite slow-wave focus" in the left posterior frontoparietal region. Admission to the Massachusetts General Hospital for further study was recommended.

On physical examination the findings were essentially as before. At this time, however, he was

disoriented in time and place. He tended to perseverate on commands. The right pupil measured 3 mm. and the left 2.5 mm. Right lower facial weakness and the falling away of the outstretched right arm and leg were again observed. The tendon reflexes were slightly more active on the right, the abdominal reflexes present and equal, and the plantar reflexes fewer. There was some loss of position sense.



FIGURE 1. *Pneumoencephalogram. Arrows point to abnormal operation of the bodies of the lateral ventricles (note the slight ventricular shift to the right).*

in the toes, more on the right. The general physical examination again was negative.

The routine laboratory studies were negative. Arteriography showed a normal vascular pattern. Pneumoencephalography revealed some shift downward of the left lateral ventricle and displacement of the third ventricle to the right (Fig. 1 and 2).

On the fifteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JAMES B. AYER* This sixty-two-year-old man gave a consecutive history over a period of six years of Jacksonian epilepsy on the right side, increasing in frequency to two or three times daily and presumably not influenced by medication.

*Member Board of Consultation (formerly chief of Neurology Service) Massachusetts General Hospital.

For six months he had been confused in thought, and latterly had shown memory loss, difficulty in comprehension, disorientation and perseveration. No note is made of motor aphasia or of agnosia. Recently, there was evidence of right hemiparesis, as shown by lagging of the right side of the face, drifting of the hand (not due to sensory loss) and stiffness of the leg, with active tendon reflexes of this side. So far the evidence indicates a progressive lesion involving the left frontal lobe, invading or

lateral ventricles. There is an abnormal separation between the superior portions of the bodies of the lateral ventricles. The inner surface of the left lateral ventricle in the region of the separation is concave. There is a definite shift of the ventricle systems to the right side. The third ventricle is displaced only slightly to the right. The lateral films (Fig. 2) corroborate essentially what has been said about the anteroposterior view, and show an indentation superiorly upon the bodies of the lateral ventricles. The arteriograms were not very helpful in this case. There was no obvious midline shift of the cerebral vessels, and I cannot be sure of a localized deformity.

DR. AYER: On seeing these films I think it is fair to say that the changes in the encephalogram could not have been brought about by any lesion except an expanding one. Although the exact location is not too evident, there is some evidence that the lesion separated the ventricles and further evidence that there was a dislocation to the right and that the ventricle on the affected side was smaller, at least in the anteroposterior view. We must now admit that, in spite of absence of symptoms of increased intracranial pressure, we have definite evidence of an expanding lesion involving the frontal and parietal regions. Against its origin in the parietal area, suggested by early Jacksonian seizures, is the tardy advent of paralysis. Against its origin at the brain base is absence of signs of pressure on optic nerves or visual pathways.

That brings us to the pathologic possibilities. The commonest causes of tumor with a focus in the frontal lobe or frontoparietal region are two: a slowly growing glioma (I think we would have to say six years is fairly long) and meningioma. Of the meningioma group about half probably arise from the sphenoidal ridge and therefore cause early symptoms referable to the base of the brain. Meningiomas may arise from the region of the falx and grow down, displacing the brain on one side or both sides, which is perhaps indicated a little by this widening of the lateral ventricle although it was not mentioned in the protocol. One of these two tumors would be by far the most likely cause of an expanding lesion in this region.

Of the other possibilities that have to be considered, we may exclude embolism, thrombosis and hemorrhage, even when encapsulated, and also subdural hematoma, always a bugbear to the neurologist.

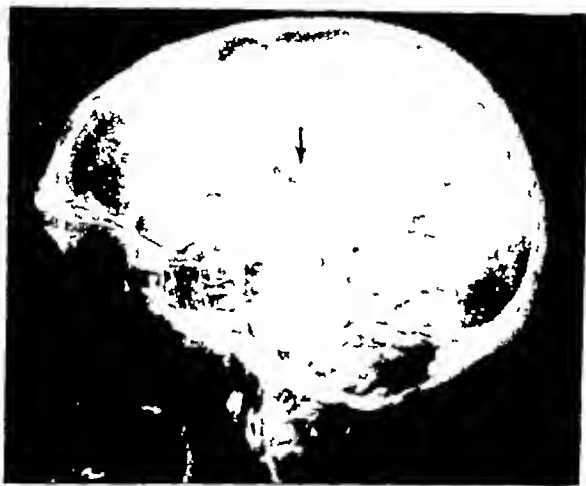


FIGURE 2. *Pneumoencephalogram. Arrow points to pressure defect on the lateral ventricles.*

compressing the motor strip. The electroencephalogram corroborates this.

Although there was no headache, no choked disk and a normal spinal-fluid pressure, the shift of the left lateral ventricle and third ventricle proves that the lesion was an expanding one. In slowly growing tumors of the frontal lobe especially, we not infrequently fail to have the clinical evidence of pressure.

May I see the x-ray films? I hate to let a single laboratory procedure influence me too much, but with a pneumoencephalogram as definite as this, we must pay heed to it.

DR. JOSEPH HANELIN: I do not believe the encephalograms have been fully described. This is an anteroposterior film (Fig. 1), showing air within the anterior portions of the bodies of the

ogist or the neurosurgeon, for these could hardly have led to such long-standing progressive symptoms

An abscess could have grown like a tumor. We have no history of underlying infection. We have no evidence for septic embolism and no sinus infection is recorded. Fever is not necessary but cells in the spinal fluid are characteristically found in abscess, nor is abscess likely to give this continuous picture.

I suppose we ought to mention a few rare things because if I make a diagnosis of something common I am often wrong at these clinics. Gumma should be considered, although it is usually close to the surface, yet it can grow inward. The serologic reaction may or may not be positive, none is given here. I should put a gumma very far down the list. Cysticercus in the frontal lobe occurs but is a surprise finding in this part of the world. Hemangioma must be considered as a possibility, but seemingly it is ruled out or made most unlikely by the angiogram which should show large and abnormal blood channels.

I am forced to say, therefore, that my choice rests between one of the two common glial tumors — probably astrocytoma which is more slowly growing than glioblastoma — and meningioma. If this was a glioma it must have grown from an intracerebral location and extended toward the vertex to separate the ventricles, it probably extended into the corpus callosum to explain some of the mental symptoms. If it was meningioma it should have originated in the meninges over the vertex and grown downward or taken origin from the falx.

The operation was probably a bone flap to remove tumor if possible, but the tumor should have been a large one, and probably not removable in toto.

DR J. C. WHITE: I am sorry that Dr. Ballantine is not here, he was the surgeon who operated. There are a few points that I would like to bring out. We thought, as Dr. Ayer pointed out, that the long history meant that this probably was an expanding tumor. Tumors, if they grow slowly enough, may become large without raising intracranial pressure. If this were an astrocytoma, we believed the chances of helping him were rather remote. If it were a meningioma, operation had a good chance of helping the seizure greatly. The astrocytomas have not responded well to operative intervention as far as seizures are concerned.

If subject to seizures, over half the patients with meningiomas are relieved of them following removal of the tumor. We discussed the problem with the family, and in view of the desperate condition they said that we should take any chance. That is why operation was done. Dr. Ballantine operated, and Dr. Bidwell assisted him.

CLINICAL DIAGNOSIS

Brain tumor ? astrocytoma, ? meningioma

DR. AYER'S DIAGNOSIS

Brain tumor left frontal, probably glioma, possibly meningioma

ANATOMICAL DIAGNOSIS

Glioblastoma multiforme of corpus callosum probably arising from astrocytoma

PATHOLOGICAL DISCUSSION

DR. ROBINSON L. BIDWELL, II: We did a bone flap on the left side, crossing the midline slightly to the right. Upon the reflexion of the dura, tumor in the left precentral region next to the midline body was immediately evident, and that was biopsied for frozen section. While we were awaiting the report, the operation was continued. As we went down, tumor outcropping on the surface was evident almost all the way down to the corpus callosum. The tumor was soft and not sharply defined at the margins. Because it was an obvious glioma and could not be excised the operation was stopped. The report that came back to the operating room was glioma, probably astrocytoma. Post-operatively, the patient did poorly, developed pulmonary symptoms and died three days later.

DR. CHARLES S. KUBIK: At post-mortem examination there were indications of greatly elevated intracranial pressure consisting of flattening of the convolutions, and temporal and cerebellar pressure cones. Coronal section at the level of the mammillary bodies disclosed a pinkish-gray tumor of the corpus callosum of rather firm, rubbery consistence involving chiefly the left side, but extending across the midline to the other side, and this accounted for the spreading apart and flattening of the lateral ventricle visualized in the ventriculogram. The tumor extended for a considerable distance laterally into the white matter of the left hemisphere and also anteriorly and posteriorly.

(Fig 3) There was no line of demarcation between tumor and brain tissue. The gross appearance was fairly typical of astrocytoma. There were numerous hemorrhages in the midbrain, these are found in most cases of increased intracranial



FIGURE 3 *Gross Specimen*
Arrows point to gross limitations of tumor

pressure with large herniations of the temporal lobe through the tentorial notch.

Histologically, the tumor was interesting. Parts of it, composed of fairly well differentiated astrocytes, would ordinarily be classified as astrocytoma,

other parts were typical of glioblastoma multiforme. The history was much longer than is usually the case in glioblastoma multiforme, and I should suppose that this was a case in which an astrocytoma had recently undergone a change to a more malignant type of tumor. We have had two or three other examples of the same kind. In a case with a twelve-year history, an astrocytoma of the cerebellum was found at operation. There was rapid recurrence of symptoms, and a second operation disclosed glioblastoma multiforme. We have had a number of cases of glioma of the corpus callosum. They have usually been associated with convulsive seizures, not infrequently Jacksonian in type, presumably because the tumor involved one hemisphere more than the other, as in this case. Another symptom, not invariably present, has been impairment of memory and confusion, one patient, however, a young man attending the Harvard Business School a good many years ago, made a very good showing in a stiff examination just before entering the hospital. In that case there was a glioblastoma multiforme of the corpus callosum much larger than this.

DR STANLEY COBB: How do you explain the original low spinal-fluid pressure?

DR KUBIK: The tumor was situated anteriorly and may have been slowly growing, and there were probably factors that we do not know about. One may also ask in a case like this whether the reading obtained at lumbar puncture represented the true pressure.

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NOBEL PRIZE IN MEDICINE

THE Nobel Prize for 1949 in medicine has been awarded jointly to two scientists, both investigating the function of the brain. Dr. Egas Moniz, a former professor of neurology in the University of Lisbon, developed cerebral angiography and made the procedure one of practical value in the diagnosis of brain tumor and blood-vessel abnormalities, and in addition devised the revolutionary brain operation of prefrontal leukotomy, later known as lobotomy, now widely used in the treatment of certain forms of mental disease. Dr. W. R. Hess, director of the Physiological Institute of Zurich University, has shown by animal experimentation the regulatory effect of the brain stem, through its peripheral projections by way of the autonomic nervous system, on such bodily processes as circulation, respiration, digestion, muscular action and psychic response. In the field of mental activity,

Hess was able to produce artificial sleep by electrical stimulation of the diencephalon, thus indicating that some psychic processes, at least, are under brain-stem control and not entirely dominated, as previously postulated, by the cerebral cortex. Although the work of Hess is less spectacular than that of Moniz, with less immediate clinical application, the research emanating from the Zurich laboratory has greatly affected the physiologic and psychiatric thinking throughout the world.

The revolutionary contribution of Moniz was announced quietly to an unsuspecting world. Lisbon was not a "center of research," such as London, Paris, Stockholm or one of a dozen other cities in Europe, where advances were being made constantly and the news quickly spread by students and visiting colleagues. Few scholars from other laboratories went to Lisbon for advanced studies, and before 1927 the name of a modest neurologist, Moniz, was virtually unknown outside his own city. So small was his audience in Portugal that he decided to present his initial paper in Paris. He journeyed to that city in the summer of 1927 and, before the Société de Neurologie on July 7, he gave his first account of cerebral angiography, showing roentgenograms of the cerebral vessels, outlined with sodium iodide, from cadavers, dogs and from a living man with a pituitary tumor.¹ The audience was astounded by the beauty of the plates and the skill of the operator in obtaining them almost instantaneously after intracarotid injection. Babinski and others, who heard Moniz's striking report, pronounced the pictures remarkable. Moniz was soon deluged with requests for information on the technic of cerebral angiography, and he responded with a second paper, outlining his experiences, which soon led to the adoption of the method in all neurosurgical and roentgenographic centers.² So carefully made were Moniz's preliminary experiments that the method devised by him prior to 1927 remains unchanged today, except for modification in the contrast mediums and the injection of the artery without previous dissection. Moniz, however, went into an even more important field than cerebral angiography and in less than a decade was able to announce his radical operation, severing the frontal lobes from the rest of the

brain, by cutting the pathways between them. Again, he went to Paris to report the results in the first 20 cases before the Académie de Médecine, on March 3, 1936.³ The idea had occurred to him about 1934, but he was encouraged to go through with the operation after a meeting of the Second International Neurological Congress, held in London in the summer of 1935. There reports were presented regarding the behavior of patients who had undergone total removal of the frontal lobes and of animals subjected to similar experimental investigations. Some of the concepts developed at this Congress, particularly those based upon the animal experiments reported from America, so impressed Moniz that, on returning to Lisbon, he devised a method of cutting the connecting pathways between the frontal lobes and the rest of the brain and had the operation carried out by his surgical colleague, Almeida Lima, as early as November 12, 1935. In less than four months, 20 case records were ready for the Paris report. In the last thirteen years, since his report in 1936, thousands of such operations, now modified into various patterns, have been carried out in many parts of the world, greatly to the betterment of patients with the more serious and prolonged types of mental aberration. A new psychiatry may be said to have been born in 1935, when Moniz took his first bold step in the field of psychosurgery.

Hess, on the other hand, has worked steadily in his physiologic laboratory, for more than twenty years, developing animal experiments on the functional organization of the diencephalic nuclei, with the particular aim of elucidating the complex functions of the autonomic nervous system, the coordinator that ensures the harmonious interplay of all vegetative organs.⁴ Taking into consideration the analyses that had accumulated throughout the years, as well as his own work on circulation and respiration, Hess⁵ attempted a resynthesis based on a view of the body organs as a system of efficiently co-ordinated functions. Of the two divisions of the autonomic system, the sympathetic section he believes plays a decisive part in preparing the subject for activity, whereas the parasympathetic system affects economy and repair. Both may exert their characteristic influences in the

psychic field, as well as on the soma. In his studies on artificial disturbance of the equilibrium between the central influences of the sympathetic and parasympathetic systems, he found a method of dampening the sympathetic control, without interfering with the activity of the parasympathetic centers. The stimulus, instead of preparing the animal for activity, induced artificial sleep, thus allowing for the possibility of better economy and repair through release of the parasympathetic forces.⁶

To psychiatry, this indication, on a sound experimental basis, that somatic influence might play a role in psychic function, gave impetus to a broadening viewpoint of cerebral action. Hess made a fundamental contribution in developing the idea that sleep was a vegetative process by which the autonomic nervous system regulated the activity of the higher cerebral functions. For this, and the rest of his great pioneering work on the physiology of the diencephalon, he, too, earned a right to the Nobel Prize.

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LET'S TALK IT OVER

BASIC agreement among professional groups on many points in the over-all problem of the nation's health has been overshadowed by controversies based on differences of opinion over certain aspects of the problem. There is real hope that give-and-take discussion across a table could rather promptly determine areas of agreement and clarify disagreements on current issues of health and medical care. The National Health Assembly in May, 1948, and the Massachusetts Health Conference in 1949 illustrate the possibilities of tangible accomplishment.

Therefore, the recent announcement of the formation of the Inter-Association Committee on Health is ground for real optimism. Participating organizations are the American Dental Association,

the American Hospital Association, the American Medical Association, the American Nursing Association, the American Public Health Association and the American Public Welfare Association, all with membership including professional workers in the health field. Each organization has as voting members three of its officers or others who carry important policy-making responsibilities. The stated objectives are to "study and discuss various phases of health care in the interest of improving the health of the nation" and to "serve as a means for the exchange of information on the programs and interests of the participating organizations to the end, that, in so far as possible, a common understanding may be reached toward the solution of health problems of mutual interest."

The principles upon which the Committee will operate are now being passed upon by the parent associations, and there is every reason to expect complete and prompt approval.

Not even the executive secretaries of these professional organizations have met together previously to discuss mutual problems. One wonders why something of this sort was not undertaken long ago. As soon as the professionals have learned to work together effectively, there will be great value in bringing in representatives of the public to give the consumer point of view. Advice from the combined group would be invaluable to Congress and other bodies now struggling to find the right answers to the nation's health problems.

THE SOUTHARD CLINIC

IN THE annals of few of the diseases of man are early diagnosis and treatment more imperative than they are in the realm of mental disorders, for in few is the possible penalty of delay more disastrous. It is for the general purposes of prevention and of early diagnosis and treatment that the federal grants outlined on a succeeding page of the *Journal* were awarded, it was for the purposes of early diagnosis and treatment that the Boston Psychopathic Hospital was created and has met with such success.

Since many of the patients who came early to the Psychopathic Hospital for diagnosis and treat-

ment were found not to require hospitalization, the outpatient department, now operating as the Southard Clinic, was established and has steadily increased its activities. Like many worthy and successful agencies, however, the Southard Clinic has found its usefulness so great that it is outgrowing its resources.

Its needs have consequently been made the subject of study by a committee of the trustees of the Hospital, and a report has been submitted that was unanimously approved by the whole board in July. The needs of the Clinic, according to this report, are not ones that should be met by still greater private benefaction as has been the case in the past. The Clinic's achievements have been instrumental in saving the Commonwealth great sums of money that would have been expended on custodial care, the Commonwealth itself is now confronted with the plain duty not only of supporting the Clinic as it at present functions but of providing for its expanded activities.

HEALTH LEAGUE PASSES

ON November 21, 1949, the Boston Health League, Incorporated, passed out of mortal being. This unusual organization, originally incorporated on June 15, 1922, has had a unique and extraordinarily useful existence. Made up of practically all the social organizations that have contributed to the preservation of health and the treatment of sickness in the city of Boston, its functions for these years have been to study the problems that have arisen, to help in their solution, and to coordinate the activities of the various groups that have composed it.

It is not because its functions are finished, however, that the Health League has shaken off its corporate bonds and passed beyond the veil. Rather is it that it might emerge, after this ordeal of dissolution, into fields of still greater usefulness as the Health Council of United Community Services. With a stream-lined program the former Health League, too, is off on the new course with the rest of the stream-lined organizations of Greater Boston.

At Pittsfield, Massachusetts, a medical student shot at a man with a revolver, with whom he had a dispute. He was immediately arrested, but liberated on bail, and then soon disappeared.

Boston M & S J, December 19, 1849

MASSACHUSETTS MEDICAL SOCIETY



COMMITTEE ON MENTAL HEALTH

The Committee on Mental Health, as part of its report to the Council next February, has included a statement on the use of federal funds for mental health in Massachusetts for the fiscal year July 1, 1949, to June 30, 1950. The sum of \$100,300 is the grant made to the Commonwealth for the current year, to be administered through the Department of Mental Health with the assistance of an Advisory Committee on Mental Hygiene and Community Activities.

The funds have been allocated as follows for training of personnel for work in mental health, \$26,140, for community mental health clinics, \$17,600, for the Catholic Boys Guidance Center of Boston, \$3750, for the Habit Clinic of Boston, \$8000, for the Child Psychiatric Clinic of Massachusetts Memorial Hospitals, \$5474, for the new community clinic in Dedham, operated in connection with the Dedham Visiting Nurse Association, \$2340, for the Massachusetts Society for Mental Hygiene, \$5000, for the Beth Israel Hospital, \$3000, for the Salem and Newton public schools, \$5000, for the Boston Floating Hospital, \$3000, and for the Massachusetts Postgraduate Training Program in Psychiatry, \$21,000.

In recognition of the short supply of psychiatrists, the last-named program has been developed as a new and special project to increase the number of psychiatrists who can be trained in the Boston area. It consists of a co-operative arrangement between teaching institutions and mental hospitals within the Commonwealth, providing for an educational director to supervise and co-ordinate the training activities and insure maximal use of facilities.

DEATHS

GOFF — Almon P. Goff, M.D., formerly of Hyannis, Massachusetts, died recently. He was in his seventy-seventh year.

Dr. Goff received his degree from University of Buffalo School of Medicine in 1897. He was formerly health officer of Barnstable County and was a fellow of the American Medical Association.

A son, a daughter and two grandsons survive.

HAWES — Alfred T. Hawes, M.D., of Lynn, died on December 2. He was in his seventy-sixth year.

Dr. Hawes received his degree from University of Vermont College of Medicine in 1901. He was an honorary member of the staff of Lynn Hospital.

A daughter, a son and two brothers survive.

MCCARTHY — Eugene A. McCarthy, M.D., of Fall River, died on December 1. He was in his sixty-ninth year.

Dr. McCarthy received his degree from Harvard Medical School in 1908. He was a fellow of the American Academy of Orthopaedic Surgeons, American College of Surgeons and American Medical Association.

His widow survives.

PHIPPS — Cadis Phipps, M.D., of Brookline, died on December 5. He was in his sixty-ninth year.

Dr. Phipps received his degree from Harvard Medical School in 1907. He was professor of medicine and head of the Department of Medicine at Tufts College Medical School and was formerly physician-in-chief of the Third Medical Service and director of the First and Third Medical Services at Boston City Hospital. He was a fellow of the American Medical Association.

His widow and a daughter survive.

WILLIAMS — Edward D. Williams, M.D., of Easthampton, died on June 25. He was in his eighty-first year.

Dr. Williams received his degree from Harvard Medical School in 1894. He was a member of the staff of the Cooley Dickinson Hospital, Northampton.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The January schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

ORTHOPEDIC CLINICS	DATE	CLINIC CONSULTANT
Haverhill	January 4	William T. Green
Greenfield	January 5	Charles L. Sturdevant
Lowell	January 6	Albert H. Brewster
Salem	January 9	Paul W. Hugenberger
Gardner	January 10	Carter R. Rowe
Brockton	January 11	George W. Van Gorder
Springfield	January 17	Garry deN. Hough, Jr.
Pittsfield	January 18	Frank A. Slawick
Worcester	January 20	John W. O'Meara
Fall River	January 23	David S. Grice
Hyannis	January 26	Paul L. Norton

RHEUMATIC FEVER CLINICS	DATES
North Reading	January 3, 10, 17, 24, 31
Fitchburg	January 4, 11, 18, 25

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

ARMY INTERNSHIP APPOINTMENTS

One hundred and ninety senior medical students have been appointed to Army internships beginning July 1, 1950, representing the Army's selections out of the 1014 candidates who applied for both Army and Air Force internships. Sixty-four of the 71 approved medical schools in the country are represented in the group of students selected, 96 per cent of whom are former servicemen. Upon graduation from

medical school each of them will be commissioned a first lieutenant in the Army Medical Corps Reserve called to extended active duty and assigned for internship to one of the ten Army General Hospitals that are approved for intern training: Brooke General Hospital San Antonio Texas Fitzsimons General Hospital Denver Colorado Gorgas Hospital Ancon Canal Zone Letterman General Hospital San Francisco California Madigan General Hospital Tacoma Washington Oliver General Hospital Augusta Georgia Percy Jones General Hospital Battle Creek Michigan Tripler General Hospital Honolulu Hawaii Valler Forge General Hospital Phoenixville Pennsylvania and Walter Reed General Hospital Washington, D. C.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Report of a Six-Months Nationwide Study of Public Knowledge about and Attitudes Toward Medical Science. By the National Opinion Research Center on a grant from the Rockefeller Foundation. 4^o, paper 25 pp. Chicago: National Society for Medical Research, 1949.

This pamphlet embodies an abbreviated report of a six-month nationwide survey of public knowledge about and attitudes toward animal experimentation.

Neuroradiology. By Alexander Orlev, M.D., F.F.R., D.M.R. &E., hon. consulting radiologist, West End Hospital for Nervous Diseases, London. 4^o, cloth, 421 pp. with 572 illustrations. Springfield, Illinois: Charles C. Thomas, 1949. \$11.50.

The author of this atlas published, in collaboration with Dr. Wakeley in 1938, a *Textbook of Neuroradiology*. Dr. Orlev states that except for the general layout, the present book has little in common with the original publication. The material covers the head, brain, spinal cord and neuropathic disturbances and is well arranged and well written. The text is concluded with a bibliography of twenty-eight pages arranged by subjects. There are good author and subject indexes. It is pleasing to note that although the book is by a British author, the printing was done in the United States and not imported. The book is recommended for all medical libraries and to all neurologists.

Care of the Surgical Patient, Including Pathologic Physiology and Principles of Diagnosis and Treatment. By Jacob Fine, M.D., surgeon-in-chief, Beth Israel Hospital, and professor of surgery at Beth Israel Hospital and Harvard Medical School. 8^o, cloth, 544 pp., with 40 illustrations and 9 tables. Philadelphia: W. B. Saunders Company, 1949. \$8.00.

This book is intended to serve the special purpose of providing a ready guide for the over-all care of the surgical patient. Dr. Fine has been aided by twenty-two specialists in the compilation of the text. The material is divided into six main divisions: general considerations, regional and special surgery, endocrine diseases and hormone therapy, coincidental medical illnesses in surgical patients, clinical and laboratory methodology, and general preoperative and postoperative care. There is a good index. The type and printing are excellent, but the use of a heavy coated paper is not justified by the few illustrations.

Coronary Artery Disease. By Ernst P. Boas, M.D., associate physician, Mt. Sinai Hospital, New York City, and Norman F. Boas, M.D. 8^o, cloth, 399 pp., with 88 illustrations. Chicago: Year Book Publishers, Incorporated, 1949. \$6.00.

This manual is one of the *General Practice Manuals*, designed for the practicing physician. The subject is well covered from the anatomy and physiology of the coronary vessels to treatment. The text is well arranged and well written.

There is a good index, and the publishing is excellent. The book should prove valuable as a ready reference source to the general practitioner. The series should be in all medical libraries.

Posttraumatic Epilepsy. By A. Earl Walker, M.D., professor of neurologic surgery, Johns Hopkins University School of Medicine, Baltimore. 8^o, cloth, 86 pp., with 20 illustrations and 6 tables. Springfield, Illinois: Charles C. Thomas, 1949. \$2.75. (*American Lecture Series*).

This monograph No. 20 in the *American Lecture Series*, discusses the condition thoroughly from pathogenesis to medical and surgical treatment. There is a bibliography of eighty titles and a good index. All the monographs are excellent, and the series should be in all medical libraries.

Care of the Infant and Child with Congenital Heart Disease: A Clinical and Physiological Study of Infants and Children. By André Courmand, M.D., associate professor, Department of Medicine, College of Physicians and Surgeons, Columbia University; Janet S. Baldwin, M.D., assistant professor, Department of Pediatrics, New York University College of Medicine; and Aaron Himmelstein, M.D., instructor, Department of Surgery, College of Physicians and Surgeons, Columbia University. 4^o, cloth, 108 pp., with illustrations. New York: Commonwealth Fund, 1949. \$4.00.

This special atlas-type monograph is divided into two parts: the physiologic methods and illustrative cases with approximate hemodynamic data. Seventeen cases are discussed in detail and illustrated with diagrams, electrocardiograms, x-ray and fluoroscopic pictures and simple schematic drawings of the circulation. A bibliography is appended to the text. There is no index. The book should be in all collections on cardiology.

Fetal and Neonatal Death: A Survey of the Incidence, Etiology, and Anatomic Manifestations of the Conditions Producing Death of the Fetus in Utero and the Infant in the Early Days of Life. By Edith L. Potter, M.D., Ph.D., associate professor in the Department of Obstetrics and Gynecology, University of Chicago School of Medicine, and pathologist at The Chicago Lying-in Hospital and Fred L. Adair, M.D. 8^o, cloth, 175 pp., with 38 illustrations and 19 tables. Chicago: University of Chicago Press, 1949. \$5.75.

This second edition of a monograph first published in 1940 has been revised, the results of the most recent research being included. Material on the Rh factor, its influence on the fetus and newborn child, and on the effects of German measles on the fetus has been added. The charts and tables also have been revised and brought up to date. The publishing is excellent in every way. The monograph should be in all large medical-reference collections.

Human Embryology and Morphology. By Sir Arthur Keith. Sixth edition. 8^o, cloth, 690 pp., with 578 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$10.00.

This standard book was first published in 1901 and has gone through six editions—good evidence of its soundness and authority. This edition has been thoroughly revised in the light of present-day knowledge of the subject. The notes and references to the various chapters have been amplified. There is a good index. The text is well printed with a good type on a light, soft, non-glare paper. The sheets were printed in Great Britain. The book should be in all medical libraries.

Neoplasms of Bone and Related Conditions: Their Etiology, Pathogenesis, Diagnosis and Treatment. By Bradley L. Coley, M.D., attending surgeon, Bone Tumor Department, Memorial Hospital for Cancer and Allied Diseases, and assistant professor of clinical surgery, Cornell University Medical College. 4^o, cloth, 765 pp., with 622 illustrations and 53 tables. New York: Paul B. Hoeber, Incorporated, 1949. \$17.50.

This large special treatise endeavors to present the current knowledge of not only true neoplasms of bone, both benign and malignant, but also the diverse group of conditions affecting the skeletal system, with which true bone tumors are often confused. The work is based on the author's experience.

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Table 2 and 3 summarize data concerning our 10 proved cases of intestinal polyposis that manifested a distinctive variety of melanin spots of the oral mucosa, lips and digits.

The ages of these 10 patients ranged from nine to thirty-nine at the time of death or first study by us. In each case, however, symptomatology referable to the intestinal polyposis had been present before, usually beginning in the teens. The pa-

Seven of our 10 patients were females, Peutz^{7 10} had 5 cases in males and 2 in females. The patient of Touraine and Couder^{17 18} was a male. For those with the entire syndrome the sexes were equally distributed. The sex was given for 24 cases of the pigment part of the syndrome as 11 males and 13 females.¹⁸ Apparently, then, the same sex distribution holds also for the patients with the pigment picture alone.

A rather wide ethnologic spread is evidenced by its occurrence in persons of American, French-

TABLE 2 Characteristics of the Pigmentation in Proved Cases of Polyposis

CASE NO.	RELATIVE INTENSITY OF PIGMENT SPOTS					PIGMENTATION ELSEWHERE ON SKIN	COLOR OF HAIR	COLOR OF IRIS	AGE AT WHICH PIGMENTATION WAS FIRST NOTED
	MOUTH	LIPS	FINGERS	TOES	FACE				
1	+++	+++	++	+	++	0	Dark brown	Brown	Early childhood
2	+++	+++	++	+	++	0	Black	Dark brown	Early childhood
3	+++	+++	+	+	+	0	?	?	?
4	+++	+++	+	+	+	0	Dark brown	Dark brown	Early in life
5	+++	+++	+	+	+	0	Dark brown	Dark brown	From infancy
6	+++	+++	++	0*	+	Light generalized negroid pigmentation	Black	Dark brown	From birth
7	+++	++	++	+	+	0	Dark brown	Dark brown	From birth
8	+++	+++	+	0	+	0	Dark brown	Dark blue	From infancy
9	+++	+++	+	0	+	0	Dark brown	Dark brown	From infancy
10	++	++	+	0	0	0	Dark brown	Dark blue	From infancy

*Pigmentation present on sole of left foot.

tients of Peutz^{7 10} and the one of Touraine and Couder^{17 18} were in an age range similar to that in our series. Apparently, the type of intestinal polyposis present in this condition becomes clinically manifest early in life.

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Italian, French, Welsh, Italian, Indo-European, Dutch and Negro family background. There are also suspected cases in English and German persons.

All our patients were of dark complexion as evidenced by brown, dark-brown or black hair and brown irides. Two had dark-blue irides. One was a lightly pigmented Negro boy. This type of complexion occurred also in the cases of Peutz^{7 10} and Touraine and Couder^{17 18} as evidenced by either their statement or by the photographs they published.

The consistency of this in all subjects may be of significance, particularly since the pigmentary

anomaly of freckles (ephelides) is common in persons of light complexion with blond, light-brown or red hair and lighter-colored irides

Pigmentation

In each case in which data were available pigmentation had been present from early in childhood to the age of twenty or more, with little or no change over the years and no very striking tendency to fade prior to that time. In Case 6 the mother noted the pigment at birth, and in Case 7

larger. Patches in the mouth were most prominent on the buccal mucosa, occasionally on the gums or hard palate and only rarely on the tongue. Those on the lips were more noticeable on the dental than outer aspect and more numerous on the lower than upper lip (Fig 1, 2, 5, 6, 7, 9, 11 and 16).

Some of the spots had a somewhat stippled appearance when examined by means of a high-power magnifying glass. This phenomenon was present in all cases when looked for (that is, Case 7, 8, 9 and 10). It is of interest that the histologic study

TABLE 3 General Information and Characteristics of the Polyposis

CASE No	AGE	SEX	NATIONALITY	FAMILY HISTORY		MALIGNANT DEGENERATION OF POLYPS TUBERCULATION OF SMALL INTESTINE	NO OF OPERATIONS FOR IN-RESECTION OF SMALL INTESTINE	LOCATION OF POLYPS			POLYPOSIS DEMONSTRATED	
				POLYPOSIS	MELANIN SPOTS			STOMACH	SMALL INTESTINE	LARGE INTESTINE	AT OPERATION	AT AUTOPSY
1	yr											
1	14	F	American	*	*	0	3	Present	Present	Present	Yes	Yes
2	39	F	French-Italian	Yes	Yes	0	1	Present	Present	Present	Yes	Yes
3	17	F	American	*	*	Present	4	Present	Present	Present	Yes	†
4	30	F	Italian	Yes	Yes	*	1	*	Present	*	Yes	†
5	9	F	Italian	Yes	Yes	0	1	Present	Present	Present	Yes	Yes
6	15	M	American (Negro)	*	*	0	3	*	Present	Present	Yes	†
7	15	F	American	*	*	0	2	Present	Present	Present	Yes	†
8	27	M	American	Yes	Yes	0	3	*	Present	*	Yes	†
9	24	F	American	Yes	Yes	0	1	*	Present	*	Yes	†
10	28	M	American	Yes	Yes	0	1	*	Present	*	Yes	†

*Not specifically searched for

†Patient living

it was noted in a picture taken at the age of three months. Peutz¹⁰ observed it in the second year of life. He believes that the mouth pigmentation persists but that some fading of the portion on the face may occur after the age of twenty-five. If only the mucosal portion of the pigmentation remains in the later years of life, it appears that the mucosal pattern is the *sine qua non* of the pigmentary part of the syndrome. Diminution of the facial portion of the pigmentation with the years may account for the difficulty that some patients had in recalling whether or not their ancestors had shown the pigmentary syndrome. Mucosal and even labial pigmentation is readily overlooked by the layman and, for that matter, in the average medical examination.

The most impressive feature in these cases was the consistent and peculiar distribution of their pigmentation. It was most striking on the lips and buccal mucosa, presenting as round, oval or irregular patches of brown or occasionally almost black pigment. A few patches may appear blue and probably represent the scattering phenomenon described by Edwards and Duntley²⁴ as being due to reflection of blue rays and absorption of red rays of the spectrum when white light is reflected from pigment particles in the dermis or corium. The patches on the lips and buccal mucosa varied from 1 mm in diameter up to 5 mm or slightly

of the lesion revealed the pigment deposit to be distributed in vertical bands through the epidermis.

Biopsy of a typical pigmented spot in Case 6 was studied histologically by Dr Lloyd W. Ketron,²⁵ who made the following remarks on the sections*:

A biopsy has been taken of a pigmented macule on the hypothenar portion of the right palm. The tissue was fixed in formalin and sections stained with hematoxylin and eosin, polychrome and methylene blue and by Giemsa's method. The patient would not permit the removal of adequate tissue to make it possible to perform silver nitrate stains.

Although clinically the pigmentation seems to have a uniform and diffuse distribution, the sections reveal that the changes occur mainly in vertical bands (see Fig 18). In these segments the following alterations are seen in the various layers in the stratum corneum there are masses of melanin conforming in size and shape with those of cells in most instances, in the basal layer there is an increased number of "clear cells" of Masson and perhaps also of the melanoblasts although none of the stains used demonstrate well the branching processes of these cells. Occasionally, one of the rete cells shows melanin granules, and a few cells in the granular layer have yellowish-brown granules. In the cutis there are a moderate number of chromatophores and occasional extracellular accumulations of melanin. One gains the impression that there is slight proliferation of the fixed tissue cells around the superficial blood vessels, which also appear to be dilated. However, because of regional differences this cannot be said with absolute certainty. These changes are similar pathologically to those seen in lentiginos. However, because of the age incidence and anatomic distribution, I should hesitate to place them in that group.

*Published here with Dr. Ketron's permission.

The above description is essentially what was noted by Touraine and Couder¹⁵ and by Siemens¹² in the study of biopsies of pigment spots in their cases. However, the vertical bands of pigment noted in our cases were not mentioned in their reports.

One patient (Case 7) had a few small pigment spots on the mucous membrane inside the nose. None of our cases had melanosis coli as evidenced by negative examination by sigmoidoscopy or inspection of the colonic mucosa in operative or autopsy specimens. However one of Peutz's patients had pigmentation of the rectal mucosa, first noted at the age of four.

To some degree pigment spots were noticed on the face in nine subjects. There are certain distinctive features. In contrast to the mucosal spots those on the face are usually quite small (1 mm in diameter or less) and are round and flat with the surface of the skin. The spots are distributed so as to be most numerous about the mouth, in some cases below the nose, about the eyes and more rarely in a butterfly pattern over the bridge of the nose. In other words they are most numerous near the orifices of the face (that is, the eyes, the nostrils and especially the lips). The spots become progressively more sparse on the forehead, temples, glabella and angles of the jaw and in the front of the ears, or, in other words, in the areas removed from the oral and nasal orifices. The facial spots usually have a darker color than freckles, and are more distinctly outlined with no tendency to coalesce as a rule. Peutz¹⁰ has been able to follow one family for thirty years and noted a tendency for the facial spots to fade progressively after the age of twenty-five, although the mucosal spots were found to persist unchanged. Facial spots in our cases varied from minimal (Case 7, Fig 9) to moderate involvement (Case 2, Fig 1). None showed the marked involvement noted in the cases of Peutz¹⁰ (Fig 14) and Touraine and Couder¹⁵ (Fig 16). Apparently, the facial distribution of the pigmentary portion of the syndrome is most varied, is not the essential portion, and may be absent or disappear as the person gets older.

When the spots were carefully looked for, each patient showed some pigmented areas on the fingers and in some cases on the toes also. To a lesser degree a few patients had spots on the hands and feet as well. On the hands the pigment spots were most numerous on the fingers, varying from a few to many, involving both the plantar and the dorsal surface. They varied in size from 1 mm to several millimeters in diameter, and were sometimes round and sometimes irregular in shape. As on the face and mucous membranes they were flat. In color they were light to very dark brown. The spots are particularly well depicted in the left hand of Case 2 (Fig 2). On clinical inspection they were much more evident than is apparent in the

photographs being obscured by high lights in some pictures.

In no case was any pigment spot elevated, vascular or hairy. In addition an important observation is that no patient showed pigmentation on any part of the body in addition to the areas noted. There was no diffuse skin pigmentation, and no accentuation of pigment in the body folds or about the nipples.

The possibility that the pigment portion of this syndrome represents ephelides (freckles) must be considered. There is much against this idea. Freckles are due to inherited aggregates of melanoblasts in the skin producing sharply demarcated

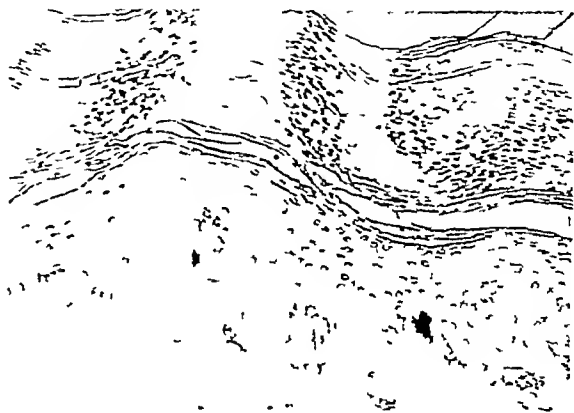


FIGURE 18 *Histologic Appearance of Melanin Spot in the Skin Obtained by Biopsy in Case 6*

Study of this section revealed that pigment particles in the epidermis occur mainly in vertical bands. Clinically, some of the spots had a somewhat stippled appearance under magnification, which could be explained by this curious histologic pattern.

yellowish-brown areas, of varying size, and often zigzag in outline. They are more obvious in spring and summer, appear early in life but not in infancy, never occur on the palms and soles, are prominent on the exposed portion of the body and are most likely to occur in persons of light complexion.

On the face, freckles are most numerous over the nose and cheeks and most sparse near the mouth and nostrils. In other words, the distribution pattern of freckles on the face is the reverse of the pattern we have described. In fact, Siemens¹² characterized the spots of the syndrome under consideration as "ephelides inversae" because of this contrast in distribution when compared with ephelides.

The most important point against ephelides is the striking and constant occurrence on the lips and buccal mucosa even when the spots are minimal on the face. During the past few years we have examined the lips and oral mucosa of several dozen heavily freckled persons of both sexes and various age groups from childhood up through the third

decade. One was a boy who had won a "freckle contest." Although heavily freckled persons may show a few lesions on the lips, in no case did we see pigment spots on the buccal mucosa, hard palate or gums.

Lentigo is essentially a localized macular area of hyperpigmentation²⁶ containing a normal number of melanoblasts. They are usually multiple, dark brown, of varying size and up to 1 cm. in diameter, occurring on the covered parts of the body as well as on the face and hands and appearing later in life than freckles do. They have no characteristic or fixed pattern of distribution. There is no known hereditary predisposition. Mucous-membrane lesions do not occur. The usually accepted description and definition of lentigo seems to exclude the idea that the pigmentary portion of the syndrome falls into this category in spite of the fact that Touraine and Couder¹⁸ refer to them as such.

Chloasma, xeroderma pigmentosa, von Recklinghausen's disease and melanosis of external origin are readily excluded from consideration.

The pigment of this syndrome is undoubtedly melanin. It may well fit into the group of melanin pigments classified by Becker and Obermayer²⁷ as "melanosis associated with increased number of melanoblasts." Its hereditary tendency (See Fig 10, 12, 13 and 15) is best explained on this basis. Is the pigment syndrome a variant of ephelides or a separate and distinct form of melanosis? The latter possibility appears most likely to us, but we have been unable to prove or disprove this thesis. In essence, the nature of the pigmentary anomaly remains obscure. Apparently, it is limited to, or most common in, persons of dark complexion.

A summary of the data concerning the pigmentation is given in Table 2.

Intestinal Polyposis

The other portion of the syndrome consists of intestinal polyposis. Apparently, in each case the polyps are distributed throughout the entire intestinal tract with their most striking clinical manifestations in the small intestine.

The features referable to the polyposis in our 10 cases are given in Table 3. The presence and nature of the polyps in each subject were definitely established by means of one or more operations on the small bowel in all cases, and in addition by post-mortem examination in 3 cases.

The symptomatology of these patients was referable chiefly to the small intestine with numerous episodes of abdominal pain and signs of minor obstruction terminating in one or more attacks of small-bowel intussusception. Surgery of the small intestine was performed on these 10 patients, varying from one to four operations each. Several patients had melena of varying degree. In Case 1 a sprue-like syndrome developed after resection

of portions of the small intestine, the procedure led to inanition and contributed to her death.

By contrast, rectal and large-bowel symptoms and signs were minimal or absent. One patient (Case 6) had significant trouble with rectal polyps, but this disappeared after the age of four, several local operations for removal of the lesions having been performed.

Just as the symptomatology pointed to the small intestine principally, operation and autopsy revealed the majority of the polyps to be located in the small intestine in all 10 cases. Furthermore, of the small intestine, it was principally the jejunum that was involved. Peutz^{7, 10} had a similar experience with polyposis involving predominantly, but not exclusively, the small intestine in his 7 cases. Four of Peutz's patients had nasal polyposis, and 1 bladder polyposis. Touraine and Couder's¹⁸ patient was said to have only rectal polyps, but adequate small-bowel studies were apparently not done.

Although predominant in the small intestine, polyposis was also present in the stomach and colon in the 3 autopsied cases in our series. Polyps were demonstrated in the colon of 3 of the living patients and in the stomach of 1. Their presence or absence in the colon and stomach of the other patients was not demonstrated. It appears that the polyposis is present throughout the entire intestinal tract but most prominent in the small intestine.

The intestinal lesions were the usual adenomatous polyps as evidenced by histologic study of resected or autopsy specimens, or both, in all 10 of our cases. This was true also of the cases of Peutz,^{7, 10} Foster^{15, 16} and van Dijk and Oudendal¹⁴ and of the rectal polyp described by Touraine and Couder.^{17, 18} A representative gross lesion of the small intestine from one of our patients (Case 7) is shown elsewhere.²⁸ In summary, then, the intestinal polyposis in these patients appears grossly and microscopically similar to generalized intestinal polyposis in persons not having the associated pigmentary syndrome.

The well known tendency for multiple polyposis of the colon to develop malignancy apparently holds to some degree for the small-bowel polyps in cases of this syndrome. In 1 patient (Case 3) in this series, 2 of Peutz's 7 patients and possibly 3 of Foster's the small-bowel lesion became malignant. The incidence of cancer here is not so great as that in the hereditary large-bowel polyposis but is distinctive enough nevertheless.

Most of the cases of multiple intestinal polyposis described in the literature^{29, 33} appear to have been limited to the colon or rectum, or both. Symptomatology in these cases is rectal or colonic. It is quite rare to find any mention at all of lesions in the small intestine in these reports. Since exploratory procedures were commonly performed, any

small-bowel polyps present would probably have been found and comment made about them

Ladd and Gross³⁴ studied the records of 92 cases of intestinal polyposis at Children's Hospital in Boston. In only 2 of these were polyps noted in the small intestine. At the Mayo Clinic, Coffey,³⁵ in a study of 29 cases of multiple intestinal polyposis noted their localization to the colon in all but 2, in which the polyps were disseminated throughout the stomach and entire intestinal tract. Apparently, multiple polyps of the small intestine are quite rare as contrasted with multiple polyposis of the large intestine. On the basis of 7000 consecutive autopsies at the Cook County Hospital, Lawrence³⁶ concluded that polyps are approximately twelve times more common in the colon than in the small intestine.

In contrast to the numerous papers dealing with polyposis of the colon and rectum is the distinct paucity of studies referable to multiple polyposis of the small intestine,³⁷⁻⁴⁰ especially cases with a heredofamilial pattern similar to that in colonic polyposis.^{14 15 41} The recent review by Ravitch⁴² on polyposis of the small intestine and polyposis of the entire gastrointestinal tract further confirms the rarity of these two varieties.

Our 10 cases, most of which were heredofamilial, seem a large number in view of the rarity with which such cases are described in the literature. Peutz's^{7 10 7} similar cases makes the number even more impressive. The additional fact that each member of this relatively large group with this unusual intestinal lesion showed a peculiar and distinctive type of pigmentation seems to us to indicate that the association is not fortuitous but of real diagnostic significance.

We have not found any report with adequate bowel studies in which the pigmentation portion of the syndrome was associated solely with large-bowel polyposis. A number of surgeons with extensive experience with large-bowel polyposis, with whom this subject was discussed, were unable to recall a personally recognized example.

*Heredity**

It is well established that multiple polyposis of the large intestine is frequently hereditary. Dukes,⁴² in an exhaustive review of the subject, concludes that it "is an inheritable disease which is transmitted by both males and females, that both males and females suffer from the disease and that the inheritance can be traced through several generations." Gates⁴³ reviewed the genetic aspects of polyposis of the large intestine and was able to discover the pedigree of a total of forty families in the literature. He concluded that the condition is a simple mendelian dominant with an occasional skip in some families.

*We are indebted to Dr. Bentley Glass of the Department of Biology, Johns Hopkins University for his assistance in the preparation of this portion of the manuscript.

As pointed out above, multiple polyposis of the small intestine or of the entire gastrointestinal tract, as seen in the syndrome discussed in this paper, appears to be an entity distinct from the more common colonic polyposis, yet our data indicate that it follows a similar genetic pattern. That this type of polyposis is likewise often hereditary there can be little question. Among our 10 cases, two families are represented by 3 cases each. In the literature there are no genealogic charts large enough to permit any conclusion regarding genetics. There are, however, reports of several families in which more than one member suffered from polyposis of the small intestine.^{7 14 15 41 44 45}

That the pigmentary portion of this syndrome is likewise hereditary is inescapable from the two family groups among our 10 cases, and from the fact that Touraine and Couder,¹⁵ in reviewing the literature on the pigmentary anomaly alone, found 31 cases, of which 22 were familial. These authors presented several genealogic charts of the pigmentary anomaly indicating inheritance as a simple mendelian dominant.

Our genealogic tables of the Dutch family (Fig 13), the Welsh family (Fig 15), the Boston family (Fig 12) and the Harrisburg family (Fig 10) not only offer proof of the hereditary nature of the complete syndrome but also permit certain other conclusions.

In the first place the syndrome appears to be inherited as a simple mendelian dominant. The involvement rate of approximately 50 per cent in the second and third generations of the Dutch family, and in the second generation of the Harrisburg family, is consistent with, although not absolute proof of, such an inheritance through the mating of persons heterozygotic for this characteristic with persons not carrying this trait. In favor of inheritance of the syndrome as a dominant is the fact that, although rare, it occurs in a large percentage of members of tainted families.

Secondly, from these four charts the characteristics constituting the syndrome appear to have a high degree of penetrance, occurring probably in the majority of those who carry the necessary factors.

Thirdly, there are no generation skips. Both males and females carry the factor, and both are affected about equally.

Further study of the genealogic tables (Fig 12 and 13) impresses one with the fact that whenever patients were actually examined and subjected to complete studies the full syndrome, polyposis and spots, occurred together in the same person. "Gene linkage" (that is, the presence on the same chromosome of a separate gene for each characteristic) will not explain the association. Snyder⁴⁶ states it thus:

The occurrence of genetic linkage between the genes for two traits does not change the association for these traits in the population from what it would be if they were not linked. Stated inversely, a correlation between two traits in a free-breeding population does not indicate genetic linkage between the genes for these traits.

The correct explanation for this syndrome as for the majority of the other hereditary syndromes must be the presence of a single pleiotropic gene responsible for both characteristics, the polyps and the spots.⁴⁷

We still await the autopsy report of a patient with the characteristic pigmentation that shows absolutely no polyps of the intestine on careful search. That the converse situation occurs seems probable. There may be several reasons for the occurrence of generalized intestinal polyposis or of polyps of the small intestine without spots. First, it must be appreciated that clinical identity does not necessarily mean genetic identity, 2 cases of polyposis clinically identical may have quite different genetic backgrounds. Secondly, in other inherited syndromes, such as Marfan's arachnodactylia, essential familial xanthomatosis and von Recklinghausen's disease, there may be in the same family great variability in the completeness or degree of expression of the individual characteristics, because of factors not well understood. That variability may, at times, be present in this syndrome, although we have no definite evidence of it. It might be subsequently demonstrated that in the same family some members show only polyposis, and some only spots.

SUMMARY

On the basis of 10 cases studied, an attempt is made to establish a syndrome that previously was not clearly identified in the English medical literature and recognized to only a very limited extent elsewhere. By supplementing our own cases with those discovered in a search of the literature and with data from personal communications, it has been possible to assemble a total of 22 proved, 5 probable and 4 possible cases.

This syndrome consists of two features distinctive melanin spots of the buccal mucosa and lips — the face and digits may be involved to a variable extent, but the mouth pigmentation is the *sine qua non* of this portion of the syndrome, and polyposis (synonyms are adenomatosis and papillomatosis) of the small intestine. The stomach, colon and rectum may be involved, but the presence of polyps in the small intestine is the constant feature of this portion of the syndrome.

Our group of 10 cases included 6 in which more

than one member of the same family was involved. Sufficient genealogic data are reported to demonstrate the hereditary nature of the syndrome, which appears to be inherited as a simple mendelian dominant. Sporadic cases also occur.

The syndrome appears to have important diagnostic significance in that the external manifestations may be of considerable value in the recognition of the intestinal condition.

As a result of several lectures on this subject, 3 additional cases have been called to our attention since the preparation of the manuscript. Two were examined in detail by one of us — 1 through the courtesy of Dr. C. Stuart Welch of the Joseph H. Pratt Diagnostic Hospital, Boston, and the other through the courtesy of the staff of the United States Naval Hospital, N. N. M. C., Bethesda, Maryland. (A colored illustration of the latter case was reproduced with the first section of this report.) All 3 patients had small-bowel polyposis, one or more operations for intussusception of the small intestine and the typically distinctive melanin spots. The last 2 cases will be reported separately by the institutions mentioned above. These additional cases provide further evidence that the syndrome is a distinct entity.

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AUREOMYCIN TREATMENT OF HERPES ZOSTER*

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AUREOMYCIN and Chloromycetin are generally referred to as agents that are effective against "viral" infections. Their demonstrated therapeutic action in this field, however, has been limited to nickettsial diseases¹⁻¹⁷ and to infections with the psittacosis-lymphogranuloma venereum group.^{1-4, 17-21} Aureomycin has also proved efficacious in cases of the so-called viral or primary atypical pneumonias.²²⁻²⁵ The etiology of the latter is still unknown beyond the demonstration that some of them may be transmissible by filtrates of materials from human cases.²⁶⁻²⁷ Neither of these agents has yet been proved to be effective against what might be called true viruses, such as those which cause yellow fever, influenza, poliomyelitis or the encephalitides.

Recently, some beneficial effects have been claimed for these antibiotics in certain skin diseases that are thought to be due to viral agents,²⁸⁻³² among which is herpes zoster.³¹⁻³² As regards the etiology of the latter, grafts of human skin onto the chorioallantois of chick embryos have been successfully infected with vesicle fluid from a patient with herpes zoster,³³ and elementary bodies have been demonstrated by electron microscopy in the vesicle fluid from various clinical types of herpes-zoster lesions.³⁴⁻³⁵ The demonstration of a therapeutic effect in this disease is therefore of considerable interest as well as of practical importance.

In this paper are presented the results of aureomycin treatment in 24 cases of herpes zoster. Although a specific therapeutic effect has not been demonstrated beyond any reasonable doubt the results are sufficiently encouraging to warrant this report.

MATERIALS AND METHODS

Cases Treated

The 24 patients included in this report were all treated during the first nine months of 1949. All had lesions that were clinically characteristic of herpes zoster. With 4 exceptions they were consecutive cases seen on the wards or in the Out Patient Skin Clinic of the Boston City Hospital. However, mild cases or those in which there was any doubt of the diagnosis or the activity of the disease were omitted. Of the 4 patients who were not treated at this hospital, 1 was a physician, another was the wife of a physician, and a third was a patient treated in another hospital by a dermatologic colleague. Detailed reports of these 3 cases were made by the physicians concerned.

Aureomycin. The aureomycin was supplied in the form of capsules each containing 250 mg. of the hydrochloride and was given by mouth, generally in doses of 1 gm. four times a day (after each meal and before retiring), and the individual doses were reduced to 0.5 gm. each after definite improvement occurred or if there was significant nausea or vomiting. Crystalline aureomycin hydrochloride was also supplied in sterile vials containing 100 mg. for intravenous use. This was given to 2 patients who refused oral therapy; individual doses of 500 mg. in 500 or 1000 cc. of 5 per cent dextrose were given by slow intravenous drip taking about an hour for each dose. (The recommended alkaline buffers were not used in these cases.)

CASE REPORTS

CASE 1. The patient was a retired physician whose herpetic lesions began in the right side of the back near the midline and extended within 7 to 10 days around the lower axillary region and reached almost to the midline. The eruption was very extensive posteriorly but tapered off as it spread to the front of the thorax. The patient paid little attention to his lesions until the middle of the 3rd week, when they became much worse and caused him considerable pain and discomfort. A month after the first appearance of the lesions and after failing to obtain relief from various remedies, he took aureomycin by mouth, a total of 7 gm. in 3 days, without any effect. He then took a course of x-ray therapy to the lesions over a period of 1 week. This gave slight relief from the pain, and the lesions began to improve but within a few days "the whole thing flared up again."

Because of the failure of the first course of x-ray treatment to terminate the disease, the patient was given a second course of x-ray treatments over a period of 2 weeks during which he also took aureomycin, 1 gm. daily, in divided doses. He improved steadily, and by the end of the 2 weeks the lesions had healed, the pain had subsided and he was able to lead a normal life again. In the course of the next 4 or 5 months, however, he had occasional recurrence of sudden, sharp pains or burning sensations, each lasting about 1 or 2 minutes and limited to the region of the eruption.

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In this case a short course of aureomycin given during the fifth week failed to alleviate the symptoms or prevent a relapse. The lesions and acute symptoms finally yielded by the end of the second month and after a second course of x-ray therapy together with small doses of aureomycin given over a period of two weeks. The role of aureomycin in this case cannot really be assessed. There were no untoward effects from the antibiotic.

CASE 2 One day after a "light" treatment at his barber's the patient began to have a burning sensation over his right eye. This continued for 3 days, after which herpes zoster appeared, first as patches of erythematous lesions over the right side of the forehead and then over the scalp. During the next 24 hours the lesions became deeply vesiculated in 2 patches, one over the right eyebrow and the other at the hairline, and these caused a constant, dull aching and marked itching. Aureomycin hydrochloride was started at this time, 1 gm orally 4 times a day for a total of 12 gm, and this produced no untoward effects. No local therapy was used. On the day after this therapy was started, 12 discrete and widely scattered vesicles, each on an erythematous base, appeared over the chest and abdomen. The right upper eyelid became swollen on this day, but no new lesions appeared in this area. The cornea and bulbar conjunctiva were spared. The pain and itching stopped, and the edema subsided on the 2nd day. The original lesions became hemorrhagic and necrotic and then dried up rapidly. All lesions were completely healed within 1 week of the first dose. There was no relapse and no post-herpetic pain.

CASE 3 This patient's first symptom was prickling pain over the left eye, which was soon followed by the appearance of groups of vesicles, one on the left side of the bridge of the nose, 2 over the eyelid and another on the forehead. Erythematous macules were also scattered over the scalp. Aureomycin hydrochloride was started 48 hours after the onset of symptoms, 1 gm was given by mouth 4 times daily for a total of 24 gm and without untoward symptoms. No local therapy was used. On the day after the aureomycin was started the left eye was swollen shut by edema of the lids, but the cornea and conjunctiva were spared, no other new lesions appeared, and vesicles did not develop in the macular lesions over the scalp. Thereafter, improvement was rapid. The edema of the lids and the pain subsided in 2 days, and within 5 days all the lesions had cleared and there was only slight itching of the scalp during this time. There were no relapses, sequelae or pain thereafter. In this case many lesions were apparently aborted by the aureomycin.

CASE 4 The first symptom was itching, and after 1 day a group of vesicles appeared on the back of the right shoulder. During the next 7 days 5 more groups of closely packed vesicles appeared around the original lesions, and severe itching persisted. Aureomycin orally was started on the 10th day, 1 gm 4 times daily. Because of nausea, the individual doses were reduced on the second day to 0.5 gm, and treatment was continued for a total of 5 days. No local therapy was used. Within 72 hours, most of the lesions had dried and were healing, and the itching had almost entirely subsided. When the patient was next seen 4 days later, all the lesions had completely cleared, and there had been no further itching. There were no relapses, nor did the patient later experience any pain. The dermatologist who followed this patient in the clinic noted in his record that he had never seen such a case clear so rapidly.

CASE 5 The patient first experienced marked itching, and within a few days an extensive vesicular eruption appeared over the right middle portion of the thorax from the spine around to the midline anteriorly. The lesions rapidly became gangrenous, and there was slight pain during the 3rd week. At that time the patient was admitted to the hospital, and aureomycin was started, 1 gm being given orally 4 times a day for a total of 25 gm. There were no untoward effects. There was remarkably rapid improvement, with considerable clearing of the lesions and subsidence of

pain within the first 2 days and almost complete clearing with minimal scarring within 6 days. Four days later, however, the patient began to have slight pain referred to the affected area. This pain increased in severity at first and then persisted with diminishing intensity for about 6 weeks without the appearance of any further lesions. It was difficult to evaluate the pain in this patient since he had no home and no resources and was obviously anxious to remain in the hospital as long as possible. In this case treatment with aureomycin was started late and appeared to have a strikingly beneficial effect on the skin lesion, but did not seem to prevent the appearance of postherpetic pain.

CASE 6 This patient first experienced discomfort in the left ear and cheek. On the following day she had general malaise and noted the appearance of a herpetiform eruption over the same area and also some enlarged cervical lymph nodes on that side. The symptoms and some shooting pains over the mandibular region increased, and the lesions advanced during the next 2 days until aureomycin was started and for about 16 hours longer. Thereafter there was steady improvement; the lesions cleared almost completely within 3 days, and the shooting pains rapidly diminished in intensity and then subsided entirely within 9 days. Neither of these recurred. The aureomycin was given by mouth, 1 gm every 6 hours for 10 doses and then 0.5 gm every 6 hours for 5 more doses. During the first 3 days, there was marked nausea for about 10 minutes after each dose, particularly when the drug was taken on an empty stomach, and during the next 2 days the nausea was continuous and there was also some diarrhea. This patient was nursing an infant during this episode, and the baby remained well.

CASE 7 The first symptom in this patient, a dental student, was a severe itching over the left flank, which caused him to scratch a good deal. On the following day the area was painful "like a boil," and during the succeeding 3 days groups of vesicles appeared lateral to the original lesions and a large patch of vesicles appeared over the upper outer quadrant of the buttock. The patient applied tincture of iodine to the initial lesion and various lotions to the entire area and also took some analgesic pills, all without preventing the progress of the lesions or of the symptoms. Aureomycin by mouth was begun on the 7th day, 1 gm 4 times a day for 2 days, and then, because of increasing nausea and frequent loose bowel movements, the dosage was reduced to 0.5 gm 4 times a day and continued until a total of 12.5 gm had been given. The untoward symptoms subsided completely on the smaller dosage. The pain and itching increased during the first 24 hours, at the end of which the lesions had already begun to improve. Within 48 hours, the vesicles had almost completely dried, and the pain had subsided. On the 4th day the lesions were almost completely healed, and only slight itching persisted for another day. There were no further lesions and no recurrence of the pain.

CASE 8 The patient first noticed a "dead feeling" and some prickling in the left flank. During the next few days groups of vesicles appeared over this area and were soon followed by sharp, knife-like pain. When the patient was first seen, at the end of the 2nd week, the lesions involved an extensive area from the spine at the level of the twelfth thoracic and first lumbar segments, around the flank and to the midline anteriorly from just above the umbilicus to the groin. There were some old lesions that were beginning to dry up and many new groups of vesicles with deep surrounding erythema that had appeared during the previous 2 days. There was severe superficial prickling and some sharp pain and paresthesias over the involved areas, and also a "clutching" feeling in the abdomen. Aureomycin was begun at this time. The patient took 750 mg by mouth 4 times a day for 3 days. No other therapy was used. No further lesions appeared after this treatment was started, and there was almost complete healing of the lesions by the end of the 3rd day. There was still slight pain at this time, but this soon subsided and there was no recurrence of pain or lesions.

CASE 9 The patient awoke one morning with a marked burning sensation over a band of the left upper portion of the chest corresponding to the cutaneous distribution of the third and fourth thoracic segments. Only after this sensation

had continued for about 5 days did he become aware of an extensive outbreak of shingles over this area. He was first seen 2 days later, when there were many groups of fresh vesicles with surrounding bright erythema. Aureomycin was started at this time, and the patient took 1 gm 4 times daily for 3 days. On the 3rd day he felt nauseated and vomited after the last 2 doses. The pain and burning cleared rapidly, and the lesions began to dry up promptly and were entirely healed within 5 days. There were no sequelae.

CASE 10 This patient first noticed some itching and a burning sensation around the left upper eyelid, which soon became red, hot and swollen. Two days later, herpetic vesicle appeared above the eyelid and spread back over the left side of the scalp. The redness and swelling of the eyelids, especially the upper lid, increased, and some of the lesions became pustular. At that time he consulted a physician, who treated him with procaine penicillin, 2 daily injections of 500,000 units each for 2 days and 1 a day for 4 more days and then sent him into the hospital. At that time the lesions involved the left side of the nose, forehead and scalp. The eye was swollen shut and the patient's temperature was 101°F. Most of the vesicles had become pustular, some of them had become encrusted, and pus oozed from the inner canthus of the eye. The left eye was swollen shut, there were blepharitis and keratoconjunctivitis with marked clouding of the cornea and 2 distinct herpetic lesions of the cornea were visualized with fluorescein. The white-cell count was 5600, with 84 per cent neutrophils. The blood nonprotein nitrogen was 107 mg per 100 cc, and the urine was loaded with pus cells. Culture of the pus from the forehead yielded a predominance of hemolytic *Staphylococcus aureus* and some *Staph. albus* alpha-hemolytic streptococci, *Proteus vulgaris* (*Bacillus proteus*) and *Clostridium perfringens* (*Cl. welchii*). A culture of pus from the left eye yielded *Escherichia coli*, *P. vulgaris* and a few staphylococci. The blood culture was negative.

The patient was treated with an aqueous solution of sodium penicillin G, 100,000 units intramuscularly every 4 hours and sulfadiazine by mouth, 1 gm every 4 hours. The latter was stopped after 3 days when he began to vomit and the sulfadiazine level was found to be 21.5 mg per 100 cc free and 26.3 mg total. The penicillin was discontinued on the next day. During these 4 days new vesicles kept appearing and there was no improvement. The blood nonprotein nitrogen was 85 mg per 100 cc. Aureomycin therapy was then started 1 gm of the hydrochloride being given orally every 4 hours and 2 drops of fresh 1 per cent aqueous solution of aureomycin borate (50 mg in 5 cc.) being instilled into the left conjunctival sac every 1 or 2 hours. The oral dose was reduced to 0.5 gm every 6 hours after 5 days because of nausea and some vomiting.

Within 24 hours of the beginning of aureomycin therapy the involved areas began to look definitely less inflamed, and no new lesions appeared thereafter. The edema of the lids began to subside on the 2nd day. By the 3rd day all redness of the skin had gone, the purulent discharge had decreased markedly and most of the lesions had become encrusted. By the 4th day healing of the skin had definitely begun, but at this time the patient complained of pain in the eye for the first time. The cornea still looked cloudy but much less inflamed, and the 2 herpetic lesions were smaller. All the swelling of the eye had subsided after 9 days, when the aureomycin was stopped. Some pain persisted and 2 days later there was a recurrence of the conjunctival infection and of a small amount of purulent discharge, but the corneal lesion continued to improve. A culture of the pus from the conjunctiva at this time showed *Staph. aureus* and *P. vulgaris*, the former sensitive to 50 microgm and the latter resistant to 200 microgm of aureomycin per cubic centimeter. The blood nonprotein nitrogen was 114 mg per 100 cc. at this time, but there were only a few pus cells in the urinary sediment.

The patient began to vomit again after the course of aureomycin therapy, and his tongue became fiery red, smooth and shiny. This cleared promptly after treatment was stopped. He was digitalized, and fluids were given parenterally, with a careful check on electrolytes. During the following 4 weeks without further antibiotic or chemotherapy, the eye gradually improved, and the nonprotein nitrogen dropped to near normal levels. At the same time the corneal opacity had cleared

almost completely and the ulcers were barely demonstrable. When the patient was last seen there was no further trace of any skin or ocular lesions. Vision was apparently unimpaired, and the conjunctivas were clear. There was no post-herpetic pain and no recurrence of lesions.

The result in this case, though not spectacular, was considered to be moderately good because of the poor prognosis that usually accompanied this type of lesion in patients of this age group.

CASE 11 The onset in this case was with pain and smarting, which was followed on the next day by the appearance of erythema and groups of vesicles scattered about the left side of the chin, jaw and temporal area. By the 3rd day, when the patient entered the hospital, some of the lesions had become hollous, and there were lesions on the left buccal mucous membrane and soft palate. Aureomycin was started on that day but was stopped because of nausea and vomiting after only 3 doses of 1 gm each had been given. Two days later there was no improvement, and several crops of new lesions had appeared, including a few on the side of the tongue. The patient was then given 500 mg of aureomycin hydrochloride in 500 cc. of 5 per cent dextrose solution by slow intravenous drip. On the following day the erythema was much less intense, and many of the vesicles had begun to dry. A second and similar injection was then given, and this was followed by oral doses of 0.5 gm 4 times a day for about 7 days. Except for occasional vomiting she tolerated this dosage well, and marked improvement followed. The lesions on the tongue improved rapidly, and the skin lesions became dry and encrusted after 2 days. The lesions had all dried up and the pain subsided after 4 days. All the lesions had completely healed within 1 week. The burning sensation in the face and the tenderness of the tongue regressed slowly during this period. After discharge from the hospital however, she began to have periodic, lancinating pains in the face, which gradually decreased in frequency and severity and finally stopped after about 2 months. After that time the site of the skin lesions was no longer discernible, but there were 2 pale, circumscribed pinkish-gray plaques without surrounding erythema on the side of the tongue.

In this case the lesions cleared, but post-herpetic pain was not prevented by the treatment.

CASE 12 Aureomycin was started in this patient as soon as she was admitted to the hospital in the middle of the 3rd week after the first appearance of her shingles. At this time there were extensive gangrenous herpetic lesions involving the right upper portion of the thorax anteriorly and posteriorly and the lower axillary region, and the patient was complaining of severe pain and burning sensations. She received 1 gm orally 4 times a day, and because of moderate nausea and some vomiting after the second day, the individual doses were reduced to 0.5 gm and continued for another 4 days. By the end of the 2nd day of this treatment there was remarkable drying of the lesions, no new ones had appeared, and there was only slight residual pain. Healing proceeded rapidly, the superficial ones were almost completely healed in 4 days, and the deeper ones healed during the next few days. After the patient left the hospital however she again had considerable burning and some intermittent shooting pains over the involved areas. For this she was given codeine and local applications of collodion by her physician. The pains gradually subsided but the burning persisted for about 3 months. After that time there was still some faint erythema at the site of the lesions, probably maintained by the local applications and irritation.

CASE 13 The herpetic lesion first appeared in this patient on the left side of the forehead 1 week after she sustained a bump on her head. During the next few days, groups of vesicles appeared on the cheek, below the eye and on the hard palate — all on the left side. By the end of 1 week, when she entered the hospital, there was extensive edema over the entire area, with intense redness surrounding the

lesions and the left eyelids were swollen. Aureomycin was started by mouth at this time, but only 2 gm was given, and the patient rejected each of them and refused oral medication. She was then given an intravenous injection of 500 mg of aureomycin hydrochloride. Within 24 hours, the lesions in the mouth had almost cleared, and there was considerable improvement in the facial and palatal lesions, the erythema and edema decreased markedly, and the vesicles appeared to be drying up. A second intravenous dose of 500 mg was given at this time and the edema and pain were entirely gone by the next day, and healing of the lesions proceeded during the next 2 days. The patient refused further medication and left the hospital. New lesions then promptly began to appear and spread over the scalp and side of the face and were accompanied by severe pain and itching. The lesions of the eye also reappeared and progressed. All the lesions healed very gradually over a period of 6 weeks, leaving scars of the skin and cornea. The latter remained hazy, and the patient's vision in the affected eye remained markedly blurred after 3 months. The pain and itching also persisted, though with diminished intensity throughout this time.

In this case marked improvement followed a brief course of intravenous injection of aureomycin, and there was a prompt, severe and prolonged relapse after the aureomycin was stopped.

CASE 14* This Negro first felt a burning sensation over the right side of the forehead, scalp and temporal region and soon noted numerous small blisters over this area. By the next day the lesions had increased in size and number, and the right eye had become red and swollen. When first seen on the 3rd day he had numerous vesicles and bullae from 1 to 13 mm in diameter over the right side of the head involving the forehead, upper eyelid and parietal region of the scalp. The lids were swollen almost completely shut. In addition, about 30 small vesicles were scattered over the rest of the body. There was only slight pain over the affected area of the head. The temperature was 99.5°F, and the white-cell count 4100. Aureomycin by mouth, 4 gm daily, was promptly started, and no other therapy was used.

In the course of the next 2 days the temperature rose to 103.8°F, and the eruption extended, with vesicles appearing on the side of the nose down to the lip, a few more bullae appeared on the forehead, and the eye was swollen shut. The lesions on the trunk, however, did not progress or increase. The tarsal conjunctivas were markedly injected, and there was some seropurulent discharge but the cornea and bulbar conjunctiva remained clear. On the 3rd day the maximum temperature was 99°F, the vesicle fluid remained clear, and no new lesions appeared. By the 4th day, the lesions had definitely begun to dry up, the eyelids were much less swollen and could be opened, the conjunctival injection subsided, and the cornea had remained clear. At the end of 1 week of treatment all of the lesions were solidly encrusted, and healing had definitely begun. Aureomycin was continued for 2 more days at 2 gm a day, and healing progressed thereafter. There were no untoward effects from the aureomycin. There was no recurrence of lesions and no post-herpetic pain.

The rapid improvement in this case was considered to be quite striking considering the severity of the lesions. It was also believed that corneal involvement may have been prevented by the treatment.

CASE 15 Five days before entering the hospital this patient noticed a rash, which began as a group of reddish raised lesions on the right side of the lower abdomen and on the right flank. This was followed by the appearance of scattered papular and vesicular lesions over the trunk and extremities. The patient experienced pains down his legs, cramps and

numbness in his toes and some burning over the lesions. When he was first seen he had several groups of lesions over the right flank and abdomen, including one large area that was gangrenous and pustular. There were also numerous scattered papules, vesicles and pustules and some encrusted lesions widely scattered over the extremities, trunk, face and neck. Two days later fresh clusters of herpes lesions, one of them a cluster of vesicles, 2 by 5 cm, with surrounding deep erythema, appeared in the right flank.

Aureomycin by mouth, 0.5 gm every 4 hours, was then started and this was increased to 1 gm every 4 hours on the 3rd and 4th days, after which the original dosage was resumed for 3 more days. The only untoward effect was slight nausea after 2 of the 1-gm doses. The pain had subsided entirely within 2 days. There was rapid improvement in the lesions, and by the 3rd day they had dried, encrusted and cleared markedly. After 6 days, when treatment was stopped, there was almost complete healing, only a few faint erythematous patches remaining. There were no recurrences of the pains or the lesions. When the patient was last seen, only a few slightly pigmented superficial scars were visible at the site of the gangrenous lesions on the lower abdomen.

CASE 16 The first symptom in this case was pain in the right shoulder radiating down the ulnar aspect of the arm—dull and aching at first but soon becoming intermittently knife-like and severe enough to interfere with sleep. On the following day the pain was worse, involving the upper right anterior portion of the chest, with radiation around to the spine, and a herpetic rash appeared on the inner aspect of the arm. On the 3rd day vesicles and erythema were also noted on the chest and back, those on the arm had become extremely painful, and the lesions had spread over most of the ulnar surface of the arm and hand, including the fingers. On the 4th day marked erythema and vesiculation covered this area and also a band about 4 cm wide across the chest from the angle of Louis around the lower axilla to the fourth dorsal vertebra.

Aureomycin was started by mouth at this time. The patient took 1 gm every 4 hours, omitting only 1 night dose. After 48 hours, the pain had almost entirely subsided, and there was only a residual mild intermittent aching. There was still moderate erythema, but the vesicles had definitely begun to dry up and no new lesions appeared. Because the patient had mild diarrhea, the individual doses of aureomycin were reduced to 500 mg each. Two days later, he was entirely free of pain, only a faint erythema was barely discernible, and there were many dry, punctate crusts over the chest and arms. There were no further untoward effects from the antibiotic, which was stopped at this time. The lesions healed rapidly, and there were no recurrences of pain or lesions.

CASE 17 The patient was being treated in the Medical Clinic with digitalis and diuretic for chronic congestive heart failure when she began one day to complain of severe pain in the left side of the chest. When she returned 2 days later, she had extensive groups of herpes vesicles, many of them bullous and each on a deeply erythematous base over an area about 8 cm wide and extending from the spine at a level of the fourth to the sixth thoracic segment around and below the axilla to the middle portion of the chest anteriorly. There was intense pain referred to this area—severe enough to interfere with sleep.

Aureomycin, 1 gm 4 times a day, was promptly started, and no other local or systemic treatment was used for these lesions. In the course of the next 3 days, the pain improved considerably, no new lesions appeared, and many of the vesicles had begun to dry up, but clear bullae were still present and there was still considerable deep erythema. Within the following 2 days the pain had almost completely subsided, and there was only a mild burning sensation over the lesions, which were now all covered with clean dry crusts and surrounded by some erythema. The patient had some nausea, and the dose of aureomycin was reduced to 0.5 gm 4 times daily. After 8 days there were only a few crusted lesions with faint erythema, and all the others showed considerable healing. The patient had 2 or 3 large loose bowel movements daily and lost a considerable amount of her edema—much more than had previously been accomplished with mercurial diuretics.

*Treated on the Dermatologic Ward of the Massachusetts General Hospital and reported through the courtesy of Dr. Walter F. Lever.

Aureomycin was stopped at this time. The patient still had some slight burning sensations during the next 3 days. A week later she again began to have rather annoying twinges of pain referred to the scarred areas, but there were no new lesions or local reactions. Aureomycin treatment was resumed for 2 days, with slight reduction of the pain but without complete relief. The itching and the twinges of pain continued for 2 more weeks.

In this case there was marked and rapid improvement in the local lesion and relief from pain accompanying the aureomycin therapy during the acute phase. The late pain was not prevented, though it may have been very slightly eased by further doses of aureomycin.

CASE 18 The patient first noted a burning sensation over the lateral aspect of the right thigh, and a pale erythematous rash appeared over this area. In the course of the next 3 days, the erythema became deeper, groups of clear vesicles appeared in the erythematous area, and the burning sensation became more severe and was soon accompanied by recurrent, intense stabbing pains. By the 7th day when he was first seen, the lesions involved the lateral aspect of the upper two thirds and part of the anterior surface of the lower third of the right thigh.

Aureomycin was promptly started and given in doses of 10 gm every 4 hours, one night dose being omitted. After 2 days the pains and burning subsided almost completely and the lesions began to dry up rapidly. On the 3rd day rather severe diarrhea, with urinary frequency and dysuria developed. The dose of aureomycin was then reduced to 0.5 gm every 4 hours and continued for 4 more days. The diarrhea and urinary symptoms were promptly relieved. The lesions, meanwhile, began to heal and by the end of a week were almost completely healed, leaving only faint erythematous areas. No new lesions had appeared.

On the morning after the aureomycin was stopped, the patient on arising noted that his tongue was swollen. The swelling subsided in about 2 hours, but he then began to have tenderness, itching, stiffness and redness of his hands, and his face felt flushed. He was given 25 mg of Thephorin (an antihistaminic), and within 1 hour the lesions and swelling cleared completely and did not recur. He had no previous history of sensitivity reactions, but he had been taking codeine and barbiturates since the onset of the shingles. It is possible that these manifestations represented a sensitization reaction to the aureomycin, although a reaction to either the codeine or the barbiturates could not be excluded since the clearing of the urticaria followed the discontinuance of these drugs as well as the aureomycin.

CASE 19 The patient first noted a burning pain beginning in the middle of the back and radiating around the right axilla to the sternum, and then an erythematous rash appeared over the right breast. On the next day she had a slight headache and malaise, she felt chilly, the temperature rose to 101°F and she was sent into the hospital. By this time the erythema had become deeper, and groups of vesicles had appeared in the erythematous areas, which now extended from the midline over the breast to the posterior axillary region. There was marked hyperesthesia over this area.

Aureomycin was started at this time and given in doses of 10 gm every 4 hours for 10 days, with no untoward effect except for some nausea on the last day. Within the first 24 hours there was a decided decrease in the hyperesthesia, and by the following day there was much less erythema and the vesicles were beginning to dry up. The pain decreased in intensity over the following 2 days but a sensation of soreness and burning in the axilla persisted for a few days longer. Meanwhile, the erythema cleared and the vesicles dried up completely and began to heal. No new lesions appeared after the aureomycin was started, and there was no late recurrence of pain.

CASE 20 The patient's wife first noticed redness over the back of his chest near the spine, and this soon extended around the right over the lower ribs to the sternum. Two days later

anorexia and general malaise developed, and the temperature rose to 100°F. At this time groups of vesicles appeared in the area of erythema to which the patient applied a lotion prescribed by his physician. By the 4th day the lesions over the involved segment had increased in number, and numerous isolated lesions resembling those of chicken pox were noted over the head, trunk and extremities but the scalp, palms and soles and the mucous membranes of the mouth were spared. Accompanying the generalized eruption there was considerable itching, anorexia and a low-grade fever. The patient continued to apply lotions to the skin and took some codeine and salicylates. Pain then began insidiously and increased in intensity after the 9th day. By the end of the 2nd week the generalized rash had completely cleared and the local lesions were beginning to dry, but the pain was still severe and there were still some acute vesicular lesions.

Aureomycin was begun at this time with doses of 0.5 gm by mouth 5 times a day and continued for 7 days. There were no ill effects except for slight nausea on several occasions. The lesions had been covered with fullers' earth by a nurse, and the healing and drying was somewhat delayed, but the pain subsided entirely within 36 hours after aureomycin was started and no new lesions appeared. Healing progressed steadily, but a slight gnawing sensation persisted for several days.

CASE 21 The patient first noted a burning sensation on the left side of his chest, and on the following day a group of erythematous lesions and some small vesicles began to appear over this region. When first seen on the 3rd day he was having intense shooting pains, and the burning sensation had become more severe. There were groups of small vesicles over deeply erythematous areas extending in a band about 6 or 7 cm wide around the left side of the chest from the middle portion of the back to the sternum, sparing only the axillary region.

Aureomycin by mouth, 1 gm 4 times a day, was promptly started. No new vesicles appeared after that. Within 2 days the pain had eased considerably, but there was still some slight burning sensation and hyperesthesia over the scapular region. After a week the lesions were all encrusted and dry, and there was no further pain and only a slight itching at night over the healing lesions. There were no untoward effects from the aureomycin, and no other local and systemic treatment was used.

CASE 22 This patient first noted intermittent, sharp, stabbing pains in the right axilla. These were followed in a few days by similar pains down the medial side of the arm and across the right side of the chest. By the 5th day, after the pain had become quite severe, a rash appeared in the right axilla and spread quickly. When she was first seen 3 days later, the vesicular, herpeticiform rash involved the axilla, the posterior surface of the upper arm and also an area extending in a band across the chest at the level of the fourth thoracic segment — all on the right side. There were also numbness and hyperesthesia on the same side involving the little finger, triceps area and ulnar surface of the forearm to the wrist. The patient had been intimately exposed to chicken pox 2 weeks before her first symptoms had begun.

Treatment was started with 1 gm of aureomycin by mouth 4 times daily. On the 2nd day, however, the patient reduced the individual doses to 0.5 gm because of severe nausea. The gastric distress continued on this dosage, and she took only 0.5 gm on the 3rd day and 250 mg on the next day. Her first return visit was on the 5th day, when the pain had almost completely subsided. Although a few new vesicles appeared in the axilla during the 1st day of treatment, most of the lesions were dry and crusted over. Further aureomycin was prescribed, but the patient took only 1 dose of 0.5 gm. The lesions continued to heal, and there was no further pain or recurrence of lesions. When she was next seen 4 weeks later only a few faint scars were discernible.

CASE 23 The patient first noted sharp, shooting pains in the left buttock radiating along the posterior aspect of the thigh to the knee. The pains continued intermittently for 2 days, and then a vesicular rash appeared, first on the left thigh and then just above the left buttock. When he was first seen on the 3rd day there were small vesicles in clusters with surrounding erythema scattered along the lower half of the medial aspect of the left thigh, and there was one

cluster just above the patella. There were also clusters of vesicles to the left of the sacral cornu and a few early erythematous, nonvesicular lesions scattered along the upper half of the medial surface of the left leg along the margin of the gastrocnemius.

Treatment with aureomycin, 1 gm orally 4 times a day, was begun at that time and continued for a total of 22 gm. There were no untoward effects. After 2 days of this therapy the pains were entirely gone, there was only slight itching, and the lesions were beginning to dry. The itching had completely subsided and the lesions were almost completely healed when the therapy was stopped. There were no recurrences of pain or lesions.

CASE 24 This patient first experienced severe lancinating pains, which began at about the angle of Louis and radiated around the right side of the chest. General malaise and ano-

patient had had one episode of vomiting 3 hours after one of the doses, so she was asked to take 0.5 gm 4 times daily. On the 4th day there was minimal burning (chafing) in the axilla, and a few small dry crusts had already appeared. On the next day the dose was again dropped to 0.5 gm 3 times a day because of nausea. By the 7th day the lesions had all dried up and were almost completely encrusted. There was one tender denuded area in the axilla but no evidence of secondary infection. The patient now complained of soreness of the tongue and mouth, but these areas looked normal. Aureomycin was stopped, and the soreness of the tongue and mouth subsided promptly. There was only slight residual burning over the axillary lesions and an occasional twinge of pain over the anterior portion of the chest in the next 2 days. Thereafter the patient was completely symptom free, and the lesions healed. There was no recurrence of the lesions and no post-herpetic pain.

TABLE 1 Relevant Findings in 24 Cases of Herpes Zoster Treated with Aureomycin

CASE NO	SEX	AGE	HERPETIC LESION		DATE BEGUN	DAYS AFTER ONSET	AUREOMYCIN THERAPY	
			CUTANEOUS SEGMENTS*	STAGE			TOTAL DOSE†	
1	M	72	T7-8	Late	Jan 10	32	70	14 0
2	M	49	V ₁ +G	Initial	Jan 25	4	12	0
3	F	65	V ₁	Initial	Feb 23	2	24	0
4	M	49	C3-4	Late acute	Feb 25	10	12	0
5	M	52	T4-6	Late	Mar 24	21	25	0
6	F	30	V ₁	Acute	Apr 1	4	12	5
7	M	25	L1-5	Acute	Apr 21	7	12	5
8	M	60	T10-L1	Late acute	May 5	14	9	0
9	M	65	T3-4	Acute	May 19	7	12	0
10	M	80	V ₁	Late acute	June 3	13	37	5
11	F	61	V ₁	Acute	June 13	3	17	11
12	F	74	T2-4	Late	June 13	17	15	0
13	F	79	V ₁	Acute	June 20	7	21	0
14††	M	72	V ₁	Acute	July 8	3	31	0
15	M	78	T10-12+G	Acute	Aug 7	7	19	0
16	M	65	C8 T1 & 4	Acute	Aug 11	4	15	0
17	F	74	T4-6	Acute	Aug 12	3	26	0
18	M	56	L2-3	Acute	Aug 18	7	20	0
19	F	72	T4-5	Acute	Aug 21	2	54	0
20	M	58	T7-8+G	Late	Aug 25	14	17	0
21	M	85	T4-6	Acute	Aug 30	5	18	0
22	F	23	T1-4	Acute	Sept 1	8	7	5
23††	M	52	L3-4	Initial	Sept 8	5	22	0
24	F	58	T1-4	Acute	Sept 8	6	16	5

*G = generalized eruption in addition to the segmental lesion. C = cervical, T = thoracic, and L = lumbar the numbers indicating the segment. V₁, V₂ and V₃ indicate the cutaneous distribution of the ophthalmic, maxillary and mandibular branches, respectively, of the trigeminal nerve (V).

† + indicates 2 separate courses or 2 separate episodes.

‡ Post-herpetic pain not prevented.

§ Generalized lesions.

¶ Patient also received aureomycin borate drops in the eye.

|| Two doses of 500 mg given intravenously on successive days, in addition to oral doses.

** Patient relapsed promptly after cessation of treatment (initial response good).

†† Negro patients.

rexia accompanied the pain. After 4 days she noted an erythematous rash over the painful area, and she felt very weak. When she was first seen on the 6th day, she still complained of recurrent pains over the right upper portion of the thorax, but these were somewhat less severe. At this time, however, there was a bullous, confluent zoster eruption with intense erythema extending from the spinous processes of the second, third and fourth dorsal vertebrae around the chest and axilla over the area between the second and fourth ribs to the sternum.

The patient was given 1 gm of aureomycin by mouth 4 times a day, but she returned the next day complaining bitterly of pain and burning over the right deltoid area and in the axilla, which kept her awake throughout the night. A few new lesions had appeared along the posteromedial aspect of the right arm, over the triceps and down to the lower third of the forearm. The patient was reassured and was asked to continue taking the aureomycin, but no analgesic was prescribed. On the following day she returned, obviously happier, and stated that her pains had virtually stopped and that she had only slight burning over the vesicular area. The original lesions on the chest had now begun to dry. The

ANALYSIS OF RESULTS

Some of the relevant data in the 24 cases are listed in Table 1. The total number of patients treated was not large, but an analysis of some of the major features will serve to bring out some of the points of interest in these results.

Effect of Sex and Age

There was a preponderance of males (15) over females (9). The patients ranged in age from twenty-three to eighty-five years, but, as usual in this disease, most of them were in the older age groups; only 5 patients were under fifty, 10 were fifty to sixty-nine and the remaining 9 were over seventy years old. There did not seem to be any correla-

tion between the sex or age of the patients and their response to aureomycin

Effect of the Stage of the Disease When Aureomycin Was Started

Patients whose skin lesions were just beginning to appear when treatment was started are listed in Table 1 as treated in the "initial" stage; those whose erythematous lesions or clear vesicles were still appearing are listed as treated in the "acute" stage, and those treated after the middle of the second week as judged from the onset of symptoms

arrested, and marked improvement followed when aureomycin therapy was resumed and the antibiotic given for two days intravenously. The good effects were maintained in Case 11 by resumption of oral therapy, but in Case 13, in which no further therapy was given, there was another relapse. Post-herpetic pain was not prevented in either of these 2 patients. There was only 1 other patient in this group (Case 17) who had post-herpetic pain in spite of what seemed to be adequate treatment and a good immediate effect on both the lesions and the pain.

TABLE 1 (Continued)

CASE No.	No. of Days After Start of Aureomycin†				ESTIMATE OF BENEFICIAL EFFECTS	DATE OF LAST FOLLOW-UP EXAMINATION
	NEW LESIONS APPEARED	LESIONS HEALED	PAIN STOPPED	ITCHING STOPPED		
1	18	2	>32	—	Probably none†	Sept. 6
2	18	7	22	—	Excellent	Sept. 16
3	0	5	2	—	Excellent	Sept. 20
4	0	—	—	—	Excellent	Sept. 30
5	0	6	20	—	Good†	Sept. 16
6	0	—	—	—	Excellent	Sept. 21
7	0	4	2	—	Excellent	Sept. 26
8	0	4	1	—	Good	Sept. 17
9	0	—	—	—	Excellent	Sept. 16
10	0	9-25	1	—	Moderate to good	Oct. 15
11	2	—	7-60	—	Good†	Sept. 16
12	0	—	4-90	—	Good†	Sept. 4
13	0	—	3-90	—	Poor†	Oct. 4
14††	1-15	>60	—	—	Good†	Sept. 26
15	0	2	—	—	Excellent	Aug. 2
16	0	2	—	—	Excellent	Oct. 10
17	0	2	—	—	Excellent	Sept. 16
18	0	2	—	—	Good†	Sept. 16
19	0	2	—	11-16	Excellent	Oct. 7
20	0	2	—	—	Excellent	Oct. 24
21	0	2	—	—	Excellent	Sept. 28
22	0	2	—	—	Excellent	Sept. 20
23	0	2	—	—	Excellent	Sept. 26
24††	0	6	—	—	Excellent	Oct. 2
25	0	6	—	—	Excellent	Sept. 22
26	1	2	—	—	Excellent	Sept. 25

or the first appearance of skin lesions, are listed as "late" cases.

By these criteria 3 patients were classified as being in the initial stage and aureomycin was started in them on the second to the fourth day. 14 others were considered to be in the acute stage and were first treated between the second to the seventh day. In all but 2 of these 17 patients the lesions and the symptoms began to show definite evidence of improvement after the first twenty-four hours of therapy. In some cases new lesions appeared during the first twenty-four to thirty-six hours but not later, except in 2 patients (Case 11 and 13), in whom oral therapy had to be interrupted. In both these cases the progress of the disease was then

In 3 patients treatment was first undertaken on the tenth to the fourteenth day, but some of the lesions were fresh and new ones were appearing at the time. They are listed as "late acute." In 2 of these patients (Case 4 and 18) the response was similar to that of the early cases, whereas in the third (Case 10) the result may be considered as quite good in view of the severity of the lesion, the amount of secondary infection and damage present when aureomycin was started and the usually poor prognosis in such cases.

Four patients were treated late in their diseases. In 3 aureomycin was started between the fourteenth and twenty-first days and their lesions and pain improved promptly, in the fourth, treatment was

started with small doses during the fifth week and there was essentially no effect. Post-herpetic pain occurred in 3 of these 4 patients, the only one among them who did not have a recurrence or persistence of pain was the one whose treatment was started on the fourteenth day.

It therefore seems that the best results were obtained in the patients who were treated on or before the middle of the second week after the first appearance of symptoms or lesions. New lesions did not appear after the first day of therapy, and then the pain subsided, the lesions dried up, and healing progressed rapidly. When treatment was interrupted early, new lesions soon appeared and pain recurred, and the progress of the lesions was again arrested by resumption of therapy. In an occasional case, post-herpetic pain appeared in spite of early and adequate treatment. In the patients treated after the end of the second week, there may have been some beneficial effect on the lesions, and there was immediate alleviation of the pain, but the post-herpetic pain was not prevented.

Effect on the Lesions

Rapid evolution and clearing of the lesions usually began within or shortly after the first twenty-four hours of aureomycin therapy. The intense erythema, when present, lessened quite promptly. The vesicles then began to dry and were usually well dried up and encrusted between two and four days after the first dose. Complete healing occurred in the great majority of cases by the seventh or eighth day, when there was left either no trace of the lesions or only a faintly erythematous scar at the site.

Appearance of New Lesions

There were 3 patients (Case 2, 22 and 24) in whom new lesions continued to appear during the first day of therapy and a fourth (Case 14) in whom such lesions occurred during the first two days while full doses of aureomycin were given. In Case 2 these were generalized lesions. In these 4 patients all the lesions began to dry up shortly thereafter, and the progress of the disease was otherwise favorable. In 3 other patients (Case 1, 11 and 13) new lesions appeared only after the early interruption of therapy.

Effect of the Site of the Lesion

There were 5 patients in this series in whom the lesions involved the cutaneous distribution of the ophthalmic branch of the trigeminal nerve, and in 1 of them the area of distribution of the maxillary nerve was also affected. One of these patients (Case 10) already had severe secondary infection of the conjunctivas with a mixture of pyogenic organisms, and there was also involvement of the cornea with herpetic lesions. In addition, this

patient had marked nitrogen retention. The progress of the herpes was promptly arrested after aureomycin was started, and the secondary infection cleared but recurred shortly after the therapy was stopped. Another of these patients (Case 13) was the one who would not continue treatment, and the lesions progressed after temporary improvement, this patient was the only one in whom there was a residuum of corneal damage and impairment of vision. The 3 remaining patients with ophthalmic herpes zoster all responded favorably and have any corneal lesions.

There was also 1 patient with in the area of the mandibular branch in whom the herpes involved the 1 of the trigeminal nerve. In both treatment was begun early. The former cleared rapidly, the 1 the one whose lesion progress was interrupted but again aureomycin was resumed.

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Generalized Herpes Zoster

In addition to the segmental 3 patients (Case 2, 15 and 16) lesions or small groups of parts of the body. In 2 patients at the time aureomycin third they appeared during the first dose was given promptly and complete was started.

There was no clinical system involvement in other patients in this however, were not done was any asymptomatic.

Effect on Pain

The immediate striking. Severe pain reduced after the first and were usually cleared five days. In a few continued with days longer.

Post-herpetic pain. Late pain was not including 3 in whom middle of the third; (Case 13) in whom not resumed. In 1 herpetic pain occurring inadequate response of the skin. In 17) an attempt was further aureomycin only two days, and

pain decreased slightly in intensity but the benefit derived was not considered sufficient to warrant continuing the therapy.

Dosage

The total dose used in these cases (excluding Case 13) varied from 7.5 to 54 gm and was given over periods ranging from three to seventeen days. Three fourths of the patients were treated for three to seven days and all but 4 received 25 gm or less. The average was about 19 gm given in six and a half days. From these observations the dose recommended at present is 4 gm daily until the lesions show definite signs of healing — usually about two to four days — and 2 gm daily for three to five days longer. The daily dose may be divided and given after each meal and on retiring.

Untoward Effects

The only evidence of any toxic effects from aureomycin was the occurrence of nausea in most of the patients. There was occasional vomiting in some, and a few had large, bulky bowel movements. These manifestations were usually encountered only during administration of the full doses of 4 gm or more daily, and nausea or vomiting was particularly apt to occur when individual doses of 1 gm each were taken on an empty stomach. They usually did not appear until after the second or third day and at a time when the lesions already showed signs of regressing. They were readily controlled in most of the patients by reduction of the dose, and only rarely were they severe enough to interfere with effective therapy. In such cases the drug could be given intravenously without untoward effects. There was 1 patient in whom angioneurotic edema of the tongue and mild generalized urticaria occurred after six days of oral administration of aureomycin but this patient also received other drugs (codeine and barbiturates), which might have been responsible for these manifestations, and the toxic effects cleared promptly after all medications were stopped.

Follow-up Study

Some of the patients were seen frequently after their aureomycin therapy was ended, and all but 1 were seen or heard from shortly before this report was completed. The last observation in these cases was made from six to eight months after therapy was started in 6 patients, after three to six months in 7, between five and ten weeks in 5 and after two to four weeks in the remaining 6 patients.

The occurrence of post-herpetic pain in 6 patients was mentioned above, this lasted from two weeks up to three months.

In only 2 patients was there a recurrence and extension of the skin lesions after therapy was stopped. One of these was the first patient treated,

and the aureomycin was started during the fifth week and only small doses were used, the other was the patient (Case 13) who refused further treatment after two intravenous doses and relapsed after leaving the hospital. This was the only patient who had residual corneal opacities and impairment of vision.

In most of the patients in whom treatment was started early the site of the original lesions was no longer discernible. In a few there were some superficial scars, and in others there was slight pigmentation in some of the sites of the lesions.

DISCUSSION

The cases presented above strongly suggest that aureomycin has a definite, beneficial effect on the course of herpes zoster. It should be emphasized, however, that although these results were obtained in consecutive cases, no parallel control series of cases was observed either without therapy or under other forms of therapy. The feature of these results that suggests a highly beneficial if not a specific effect is the fairly regular and characteristic response in all patients receiving adequate amounts of this antibiotic in the early or active stage of the disease.

It seems highly unlikely that this benefit is wholly the result of an effect on secondary bacterial infection. Although such an effect undoubtedly played a part in some of the cases there was no evidence of bacterial infections in most of the patients. Furthermore, other potent antibacterial agents, notably penicillin, have not had any similar effect although they may have favorably influenced the progenic component of the lesions. Perhaps more significant is the fact that new herpes-zoster lesions have not developed during aureomycin therapy except during the first day or so, although such lesions have appeared after treatment was interrupted too soon.

Mention has been made by one reliable observer¹⁶ that herpes zoster has developed during the course of aureomycin treatment for other infections that occurred after nephrectomy. In a personal communication Schoenbach has mentioned another patient who was treated for a urinary-tract infection following a left nephrectomy and in whom "herpes zoster" developed on the right lower quadrant and back on the seventh day of aureomycin treatment (2 gm daily) and 2 weeks after the nephrectomy. In view of these cases, the estimate of the specific value of aureomycin in this disease, as suggested by the experience in the present series of cases, may have to be revised.*

Results similar to those noted in these cases have been reported from Chloromycetin in 4 cases that were treated in the acute stage. Post-herpetic pain

*Schoenbach, in a personal communication, has also observed 5 patients with typical herpes zoster who showed a rapid clinical improvement similar to those described in this paper. These 5 patients had not had any operations.

started with small doses during the fifth week and there was essentially no effect. Post-herpetic pain occurred in 3 of these 4 patients, the only one among them who did not have a recurrence or persistence of pain was the one whose treatment was started on the fourteenth day.

It therefore seems that the best results were obtained in the patients who were treated on or before the middle of the second week after the first appearance of symptoms or lesions. New lesions did not appear after the first day of therapy, and then the pain subsided, the lesions dried up, and healing progressed rapidly. When treatment was interrupted early, new lesions soon appeared and pain recurred, and the progress of the lesions was again arrested by resumption of therapy. In an occasional case, post-herpetic pain appeared in spite of early and adequate treatment. In the patients treated after the end of the second week, there may have been some beneficial effect on the lesions, and there was immediate alleviation of the pain, but the post-herpetic pain was not prevented.

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There was also 1 patient with involvement of the area of the mandibular branch and another in whom the herpes involved the maxillary branch of the trigeminal nerve. In both these patients treatment was begun early. The lesions in the former cleared rapidly, the latter (Case 11) was the one whose lesion progressed when treatment was interrupted but again improved when aureomycin was resumed.

The remaining patients all had involvement of the trunk and extremities.

Generalized Herpes Zoster

In addition to the segmental lesions there were 3 patients (Case 2, 15 and 20) who had isolated lesions or small groups of vesicles over all other parts of the body. In 2 patients they were present at the time aureomycin was started, and in the third they appeared during the first few hours after the first dose was given. These lesions all cleared promptly and completely after the aureomycin was started.

There was no clinical evidence of central-nervous-system involvement in any of these or any of the other patients in this series. Lumbar punctures, however, were not done to determine whether there was any asymptomatic involvement.

Effect on Pain

The immediate effect on the pain was quite striking. Severe pain and itching were markedly reduced after the first twenty-four hours of therapy and were usually completely relieved in four or five days. In a few patients, however, the pain continued with diminishing intensity for a few days longer.

Post-herpetic pain was mentioned above. This late pain was not prevented in 6 of the patients, including 3 in whom therapy was started after the middle of the third week of the disease and a fourth (Case 13) in whom therapy was interrupted and not resumed. In the other 2 patients the post-herpetic pain occurred in spite of early and seemingly adequate therapy and in spite of a good response of the skin lesions. In 1 of the latter (Case 17) an attempt was made to influence the pain by further aureomycin therapy. This was given for only two days, and the patient stated that the

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PROSTHESIS FOLLOWING HEMIPELVECTOMY*

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A MAJOR problem in the rehabilitation of patients subjected to hemipelvectomy has been the adaptation of a suitable prosthetic appliance. Owing to the rarity of this type of amputation both the surgeon and the artificial-limb manufacturer have had few opportunities to clarify the problem. The purpose of this report is to present

in 1916. Later reviews of the subject with presentation of cases were recorded by Judin,³ Gordon-Taylor,^{4, 5} Leighton,⁶ Morton,⁷ Sugarbaker⁸ and Pack et al.^{9, 10} The last authors, in their comprehensive work on exarticulation of the extremities for cancer, reaffirm the idea that a useful prosthesis has never been devised for these patients subjected

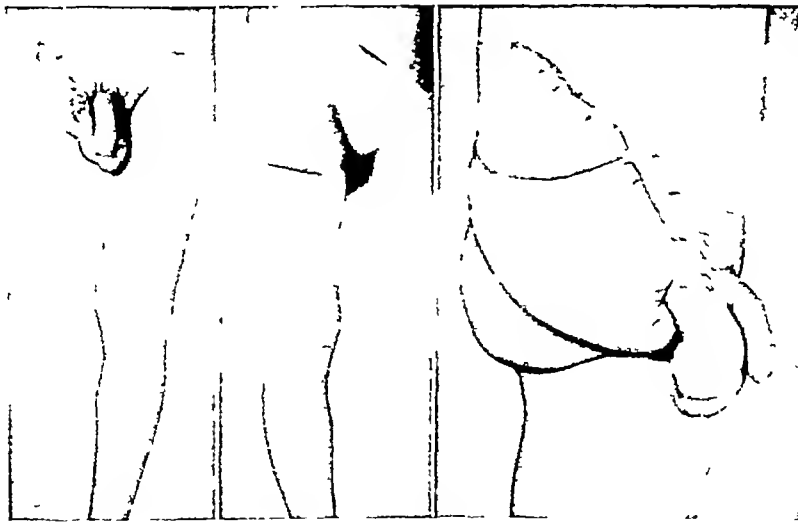


FIGURE 1 Extent of Amputation

an efficient prosthetic appliance of this character and to record a case of its successful use.

In the last half century 138 cases of hind-quarter amputation have been reported in the literature. This radical surgical procedure was first performed successfully in 1895 by Girard¹ and later standardized by the methodical work of Hogarth Pringle.²

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to hemipelvectomy. Perforce, the patient learns to sit on the remaining ischial tuberosity and becomes adept in the use of crutches.

It is recognized that the successful adaptation of a prosthesis in these cases is difficult and wholly dependent upon the personality and physical status of the patient. A lithe, young, energetic and co-operative patient naturally possesses greater potentialities for complete rehabilitation than the apathetic, more passive subject. The case reported below represents the successful prosthetic reha-

was not affected by the Chloromycetin in 2 other cases³² Initial experiences in 3 early cases of herpes zoster treated with Chloromycetin in this clinic seem to substantiate these findings

It is to be borne in mind that many other agents have, in the past, been claimed to have striking and specific effects in this disease³⁷ These will not be reviewed here Suffice it to say that none of them have thus far gained acceptance or wide use as specific therapeutic agents for herpes zoster Further experience will be necessary to ascertain the true value and place of aureomycin (and Chloromycetin)

Brief mention may also be made of aureomycin in herpes simplex Claims have been made of beneficial effects from this antibiotic in patients with skin lesions considered to be due to the virus of herpes simplex^{29, 31} (herpes labialis and Kaposi's varicelliform eruption) We have observed several cases in which the lesions of herpes labialis healed fairly rapidly under systemic treatment with aureomycin Some of these patients believed that they were definitely benefited by the aureomycin in that their lesions healed much more rapidly than they had in previous similar episodes Most of these patients, however, had coincident impetiginous lesions or superimposed staphylococcal and streptococcal infections, and the improvement could be interpreted as a result of the effect on these secondary infections

As opposed to these apparently favorable results, at least 4 patients have now been observed in this hospital in whom characteristic herpes labialis appeared and extended during treatment with full doses of aureomycin given for acute bacterial infections³⁸ The latter observations are much more significant and render it unlikely that aureomycin has a specific action against herpes-simplex infections It is possible, of course, that multiple agents are involved in the etiology of these types of lesions or that there are strain differences in the susceptibility of the herpes virus to aureomycin This possibility must also be considered, of course, in cases of herpes zoster

SUMMARY

The relevant findings in 24 cases of herpes zoster treated with aureomycin are presented

Aureomycin appeared to halt the progress of this disease and to bring about rapid healing of the lesions Vesicles dried up and became encrusted in the first two to four days after treatment was started and proceeded to heal rapidly and completely thereafter In occasional patients new lesions appeared during the first day of treatment but not later unless the therapy was interrupted

The pain accompanying the acute lesions also subsided after the first day of therapy Post-herpetic pain rarely occurred in the patients whose treatment was begun early and was maintained in adequate dosage, but it was not prevented in the pa-

tients in whom treatment was begun more than two weeks after the first appearance of the lesions

The oral dosage found to be effective in these cases was 4 gm daily (1 gm after each meal and at bedtime) for two to four days, or until the lesions were well dried and encrusted Half this dose is given for an additional three to five days and may also be used throughout when the larger doses are not tolerated Intravenous doses of 500 mg daily likewise appear to be effective and may be used if the oral dose is not well tolerated The optimum intravenous dosage, however, was not ascertained

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it was found necessary to displace the center of gravity of the artificial limb several inches laterally to force the patient to shift his weight to his sound limb after initially bearing weight on his prosthesis. In this manner any tendency to shift weight toward the prosthetic or unstable side of the body in motion was effectively minimized.

With the foregoing type of prosthesis the patient rapidly became ambulant and manifested complete satisfaction with his appliance. The extent of the amputation, the patient with the prosthesis applied and the appliance itself are shown in Figure 1 to 3. At present he is able to walk without the aid of a cane or crutch, with only a moderate limp resulting from the required shortening of the appliance. He is able to ascend and descend several flights of stairs with ease. The only apparent disadvantage is that he requires considerable aid in attaching his prosthesis, which is bulky and difficult for him to apply without assistance.

SUMMARY

Adaptation of a prosthetic appliance after hemipelvectomy has proved a difficult problem in the

past. This is apparent in a review of the current literature. A case of chondrosarcoma of the acetabulum in which the patient was subjected to hemipelvectomy, with subsequent complete rehabilitation as a result of the development of a suitable and efficient artificial limb, is presented.

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MANAGEMENT OF TRIAL LABOR*

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OBSTETRIC patients usually fall into three broad clinical groups. First, a fairly large number have normal pelvic measurements and satisfactory labor and deliver without difficulty. Secondly, a very small number have pelvic measurements that make normal delivery impossible, with cephalopelvic disproportion evident both clinically and by x-ray examination — it is readily apparent that elective cesarean section is indicated for these patients. Thirdly, a large number have what might be termed "border-line" pelvic measurements that place them in the mind of the examiner as suspects for cephalopelvic disproportion. The prognosis for delivery through the pelvis in the third group may be somewhat doubtful. It is this particular group that I should like to discuss, because conservative management will result in a high percentage of uncomplicated pelvic deliveries if the patients are given a trial labor.

It may be well to recall that there are five components of cephalopelvic disproportion: the size and shape of the pelvis, the size of the fetal head, the position and presentation of the fetus, the degree of molding to which the head is subjected, and the force of the labor pains. Of these, only the

first, the size and shape of the pelvis, is susceptible to accurate measurement before labor begins. Current methods of fetal cephalometry have not proved satisfactory.

The final position and presentation cannot be adequately determined until the onset of labor, because an unfavorable presentation is often converted into a more favorable one by the forces of labor. The most important factor in determining the outcome in the group under discussion is the quality of the labor pains. One has no way of pre-determining the nature of the labor. The quality of the labor pains is important, because satisfactory labor will frequently more than compensate for small pelvic diameters, and a normal pelvic delivery will result.

I do not wish to place too much emphasis on x-ray pelvimetry, but when the question of cephalopelvic disproportion arises it is very helpful toward intelligent management of the situation. X-ray examination of the pelvis is indicated if the clinical examination discloses such unfavorable signs as the ability to touch the promontory easily on vaginal examination, angulation of the sacrum, narrowing of the outlet and failure of a primipara to engage at term, to mention only a few.

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bilitation of an agile and earnest young man who made a rapid recovery after hemipelvectomy for a chondrosarcoma of the acetabulum

CASE REPORT

F R, a 24-year-old Navy veteran, was admitted to the Orthopedic Service of the Veterans Administration Hospital, West Roxbury, Massachusetts, on April 21, 1947, complaining of recurrent pain in the right hip of 4 years' duration following minor trauma. This pain had a tendency to develop while the patient was at rest, particularly in the sitting position.

The past and family histories were noncontributory.

Physical examination was entirely negative except for limited motion of the right hip. X-ray study revealed a destructive cystic process involving the right acetabulum. Pertinent laboratory studies revealed only an elevated blood cholesterol of 240, 275 and 289 mg per 100 cc, and an alkaline phosphatase of 5.3 Bodansky units. X-ray films of the chest and a bone series were normal.

Biopsy of the lesion on May 5, 1947, demonstrated numerous, free, cartilaginous bodies within the joint space. A pathological diagnosis of chondrosarcoma was made on

that time adequate shrinkage of the stump had occurred and sufficient consolidation of tissue had taken place so that weight bearing was possible. It should be realized that no true stump was actually present but only a soft-tissue mass composed of anterior and posterior abdominal parietes, which provided weight-bearing surface.

The prosthesis itself was of the conventional willow-wood type with the usual knee and ankle articulation designed in the standard fashion of all artificial-limb manufacturers. In addition to

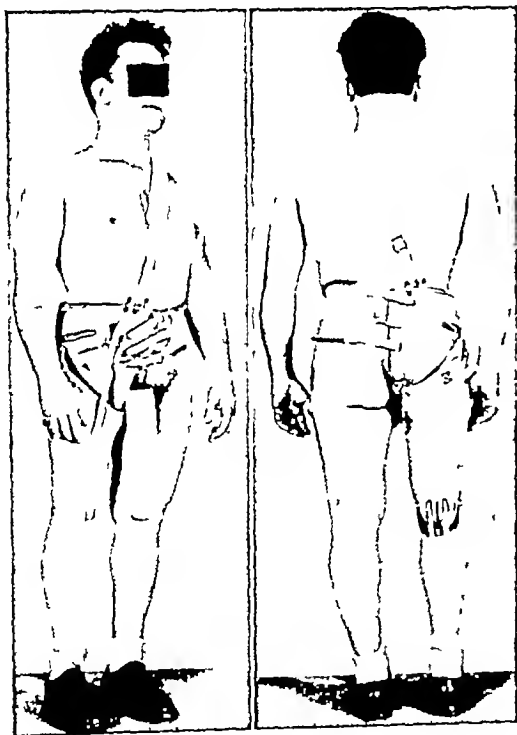


FIGURE 2 Patient with Prosthesis in Place

examination of this material. At a later date a right sacro-iliac disarticulation was performed, and the patient made a remarkably rapid and uneventful recovery. He was soon able to be about on crutches with surprising agility. Pathological examination confirmed the original diagnosis and disclosed disease arising in the acetabulum with invasion of the ilium to within 1 or 2 mm of the pelvic surface. There was also moderate involvement of the femoral neck and joint capsule. Repeated follow-up x-ray examinations of the chest have been negative for metastasis.

DISCUSSION

The prosthetic appliance was not provided for the patient until six months had elapsed. During

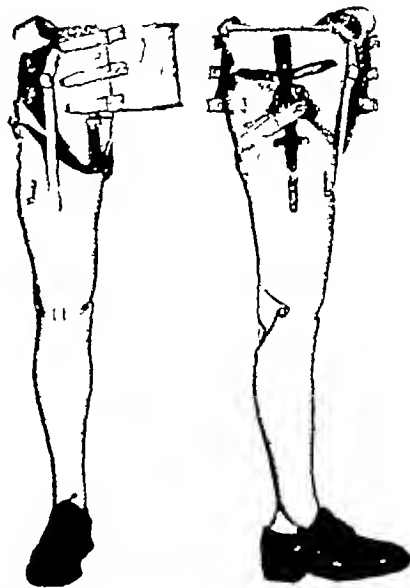


FIGURE 3 Photograph of the Prosthetic Appliance

these articulations, a steel hip-joint device, which locked in extension and could be readily released for flexion of thigh in the sitting position, was developed. A preliminary cast of the amputation site enabled the manufacturer to evolve a "leather bucket" composed of molded laminated cowhide, which closely approximated the contours of the stump. This was fashioned so that weight was borne on the soft-tissue mass anteriorly, laterally and inferiorly, without direct pressure on the coccyx or opposite ischial tuberosity. To ensure union of the prosthesis and patient there was a wide abdominal belt fastening anteriorly, with the added support of a broad shoulder strap applied over the left shoulder.

The problem of stability of the patient in motion was solved in an ingenious manner by the limb maker. It was recognized that the sound limb of the subject was the keystone of stability and function, and therefore the artificial limb was so designed as to compel the subject to utilize it as a secondary aid in locomotion rather than a primary one. Thus,

observed that the hematologic response to folic acid paralleled that which followed treatment with concentrated liver extract in cases of macrocytic anemia, but the rate of regeneration was greater with a potent liver extract. Berk et al.¹⁷² reported the reticulocyte responses and initial rises in the red-cell count and hemoglobin of 12 patients with pernicious anemia treated with daily doses of 10 mg of folic acid intramuscularly to be comparable to those seen with purified liver extract. In general the evidence is against folic acid in cases of Addisonian pernicious anemia and nontropical sprue. Hall and Watkins¹⁷³ found that the maximal reticulocyte response was lower after folic acid therapy as compared with liver extract, and that in 3 cases the red-cell count did not increase above 3,500,000 despite prolonged treatment with folic acid. An unsatisfactory hematologic response to folic acid was observed in 9 of 10 patients with the sprue syndrome, but these patients had a normoblastic bone marrow, although their peripheral red blood cells were macrocytic.¹⁷⁴ A similar observation was made by Weir and Comfort.¹⁷⁵ There are even reports of hematologic relapses in Addisonian pernicious anemia during prolonged therapy with adequate doses of folic acid¹⁷⁶⁻¹⁷⁸ but with subsequent remissions after administration of liver extract. Jones et al.¹⁷⁹ also record a case of nontropical sprue in which a hematologic relapse developed after good initial response to folic acid and the patient subsequently improved with vitamin B₁₂ therapy.

In contrast to these two diseases, folic acid has proved to be effective hematopoietically in other types of megaloblastic anemia that are refractory to liver extract and vitamin B₁₂.¹⁸⁰⁻¹⁸³

The failure of folic acid to alleviate or prevent the neurologic sequelae of Addisonian pernicious anemia has been reported by so many investigators that nearly all clinicians agree with the advice of an editorial in the *Lancet*,¹⁸⁴ which states, "The practical lesson is clear and agreed: folic acid whether alone or with liver extract must not be given to patients with pernicious anaemia." The chief controversy over the use of folic acid concerns its possible toxic effect on the central nervous system. Neurologic manifestations of pernicious anemia appear with much greater frequency after treatment with folic acid than in untreated cases.¹⁸⁵ This complication after folic acid therapy is also more precipitous in nature and involves the posterior columns of the spinal cord more completely than the lateral columns.¹⁸⁶ Such observations suggest that the resultant effect of folic acid on the central nervous system is not identical with "combined-system disease."

Neurologic complications of folic acid therapy are not limited to Addisonian pernicious anemia alone. An occasional case of peripheral neuritis

after folic acid therapy for other macrocytic anemias has been reported.¹⁸⁷⁻¹⁸⁸

Some investigators have believed that folic acid was actually toxic to the central nervous system.¹⁸⁹ This seems to be a minority view, because of the small number of cases other than Addisonian pernicious anemia that have had neurologic complications after prolonged folic acid therapy.¹⁸⁹⁻¹⁹⁰ The occasional case of glossitis or other characteristic signs of vitamin deficiency that appear during the prolonged administration of folic acid is explained on the basis of vitamin imbalance. In view of these observations, it is probable that the peripheral neuritis and possibly the central-nervous-system symptoms associated with folic acid therapy actually represent another manifestation of vitamin imbalance rather than true toxicity.¹⁸⁸

The mechanism whereby folic acid produces a hematologic response is not known. In fact, there is no evidence that there is a dietary deficiency of folic acid in these diseases, but perhaps an impairment in the utilization of folic acid. On the other hand, in the nutritional deficiency disease, tropical sprue, the remarkable effectiveness of folic acid, which has been so well established by Suarez et al.,¹⁹¹ seems to indicate that tropical sprue represents a true primary folic acid deficiency. The effect of folic acid in nontropical sprue has been clinically beneficial according to some observers.¹⁷⁴⁻¹⁹² Darby and his associates¹⁹² noted the return of glucose tolerance tests toward normal in 5 out of 6 cases of nontropical sprue after folic acid therapy, and improvement in the vitamin A absorption curve in 2 cases. Other investigators have not observed any striking benefit of folic acid in cases of nontropical sprue.¹⁷⁵⁻¹⁹³ This difference in result may be due to the fact that cases of idiopathic steatorrhea that do not respond to folic acid are not nontropical sprue but represent fatty diarrhea from other causes.¹⁹² It is possible, however, that some cases of nontropical sprue do not respond to folic acid because the disease has reached an irreversible stage. The mode of action of folic acid in nontropical sprue is not replacement therapy for a deficiency state, since most of these patients have had an adequate diet, however, the therapeutic effect of folic acid may represent a pharmacologic manifestation.

As a result of the investigations that have appeared since Sargent's⁸ review, the place of folic acid in nutrition is now more clearly defined. The vitamin is effective in certain liver-refractory macrocytic anemias and is almost specific for the malnutrition state of tropical sprue. The neurologic complications, glossitis and pellagra associated with folic acid therapy seem to be best explained by vitamin imbalance rather than the toxic effects of folic acid. This member of the vitamin B complex does not have the same hematopoietic effect as liver in the treatment of Addisonian pernicious

The management of a trial labor is essentially the management of *any* labor in addition to the adherence to certain definite principles from the outset. It is important in the conduct of a trial labor to set some reasonable time limit on the length of the trial period. I believe it is fair to state that if after twelve to fifteen hours no progress has been made, the termination of labor by abdominal delivery should be considered. Many factors enter into an evaluation of whether the patient has or has not made progress. Three significant signs or symptoms indicating progress are — effacement and dilatation of the cervix, increase in the strength and frequency of the labor pains and descent of

the head. The last is positive evidence that the patient has made progress.

Lateral films taken at intervals during labor offer concrete proof of whether or not the head was descended. Progress or the lack of progress is the decision that the obstetrician must make as the end of the trial period approaches.

I should like to offer a word of caution regarding strict asepsis during labor. It should be constantly remembered throughout a trial labor that the patient is a potential candidate for cesarean section, and therefore, all examinations should be conducted aseptically. The number of rectal examinations should be reduced to an absolute minimum and not more than one sterile vaginal examination should be permitted during a trial labor.

MEDICAL PROGRESS

VITAMIN SUPPLEMENTATION IN HEALTH AND DISEASE (Concluded)*

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NEWER VITAMINS

During the last four years, an important place in medical literature has been given to the discovery and therapeutic uses of three newer vitamins that promise much for man. These three substances are folic acid, vitamin B₁₂, and rutin or vitamin P. At present it is impossible to ascertain whether the clinical response to these supplements is due to alleviation of a deficiency of the specific newer factor or whether benefit results from a pharmacologic effect.

Folic Acid

The fast-moving history of the discovery, identification, synthesis, physiology and therapeutic uses of folic acid was well reviewed by Sargent⁸ in 1947. To paraphrase his summary, folic acid is known chemically as pteroylglutamic acid, which is the active form of this newer member of the vitamin B complex. The vitamin occurs in many foods such as liver, green vegetables, kidneys and yeast, but it is usually in the physiologically inactive conjugated form, pteroylheptaglutamic acid (vitamin B₉ conjugate). An enzyme, vitamin B₉ conjugase, which liberates the active pteroylglutamic acid, is present in many mammalian tissues. Foods contain a conjugase inhibitor, which impedes the hydrolytic activity of the vitamin B₉ conjugase.

The amount of pteroylglutamic acid in the ordinary diet is far less than the usual therapeutic level of folic acid, which is estimated at 5 to 10 mg daily.

Pteroylglutamic acid has been effective in promoting a hematopoietic response in the various macrocytic anemias, in some of the sprue syndromes and in certain cases of "chronic diarrhea" due to nutritive failure. The natural heptapeptide, pteroylheptaglutamic acid, was found to be ineffective in Addisonian pernicious anemia, whereas the synthetic pteroylglutamic acid was utilized. The explanation of this observation is that patients with Addisonian pernicious anemia are unable to neutralize the conjugase inhibitor. Initial enthusiasm for the use of folic acid in Addisonian pernicious anemia was soon dampened by reports of the explosive appearance of neurologic complications in such cases, and for this reason the management of Addisonian pernicious anemia with pteroylglutamic acid was not recommended.

Folic acid was found to have no effect on the anemias associated with iron deficiency, cancer, leukemia and lymphoma, nor on aplastic anemia, agranulocytosis and thrombocytopenic purpura.

The numerous reports on folic acid that have appeared since Sargent's review primarily confirm the findings already summarized, but some clarify certain doubtful points and more definitely define the final place of folic acid in therapeutics.

There has been considerable discussion of the relative hematopoietic effect of folic acid as compared with liver extract. Frommeyer and Spies¹⁷¹

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of its diuretic action in 12 of 16 patients with normal blood pictures²⁰⁷ The investigators who report this finding speculate that large doses of vitamin B₁ may cause a vasodilation owing to the action of cobalt

The minimal and optimal dosage of vitamin B₁ has already become the subject of considerable difference of opinion On the basis of the original reports, it was believed that 1 gamma of vitamin B₁₂ was approximately equal to 1 *U S P* unit of liver extract,¹⁹⁴ and bioassay of several commercial liver extracts showed that vitamin B₁ might have an even greater potency¹⁹⁴ Subsequent clinical trials showed that 1 gamma of vitamin B₁ per day produced a maximum reticulocyte response in some cases^{200 201} and that, by comparison of the rates of increase in red-cell count, 1 gamma of vitamin B₁ was approximately equal to 1 *U S P* unit of liver extract¹⁹⁵

Sturgis²⁰⁸ reports that as little as 0.45 gamma of vitamin B₁ per day will produce a definite although substandard hematologic response The general consensus is that the rate of utilization of vitamin B₁ approximates 1 gamma per day and with daily administration at this level, there is no storage of the vitamin¹⁷⁹

Some investigators believe that the reticulocyte response does not parallel the rate of hemoregeneration and that the latter is a truer measure of vitamin B₁ activity^{179 209} By such determinations it is shown that more than 1 gamma of vitamin B₁ per day is necessary for a maximum rate of erythropoiesis,¹⁷⁹ and Jacobson²⁰⁹ believes that 3 or 4 gamma per day is needed to achieve the maximum rate of red-cell regeneration

Jacobson²⁰⁹ also suggests that 3 or 4 gamma of vitamin B₁₂ may be needed to equal the biologic activity of 1 *U S P* unit of liver He explains this observation, which is at variance with the bioassay measurement of vitamin B₁ in terms of *U S P* liver units,¹⁹⁴ by postulating the presence of accessory factors in liver extract that may be important for the therapeutic activity of vitamin B₁²⁰⁹

The controversy about the *U S P* liver-unit value of 1 gamma of vitamin B₁₂ appears to be merely one of definition — namely, the measure of 1 *U S P* unit of liver Since crystalline vitamin B₁ is administered in weighed amounts, it can be expected to produce more uniform clinical results than liver extract, whose potency may be rather variable because it is established by bioassay Moreover, the differences of opinion about the values for the minimal and optimal doses of vitamin B₁₂ could be explained easily on the basis of the differences in requirement among the various patients with pernicious anemia A safe working rule might be to administer 15 to 25 gamma of vitamin B₁

per week until the red-cell count had returned to normal and then to maintain the patient on a dose approximating 1 gamma per day

Vitamin B₁₂ has other advantages over liver extract in that the vitamin, which seems to be non-allergenic, can be safely administered to patients who are sensitive to liver extract,²⁰⁴ and much larger amounts of the antipernicious-anemia factor can be given in a single dose of vitamin B₁₂

The specificity of pteroylglutamic acid for certain anemias and of vitamin B₁₂ for others offers promise of a better understanding of the nature of the macrocytic anemias

Rutin (Vitamin P)

Vitamin P, first described in 1936 as a possible food factor associated with the integrity of the walls of blood capillaries,²¹⁰ did not get an adequate clinical trial until 1944, when Griffith et al²¹¹ reported that rutin had restored the increased capillary fragility to a normal state in 8 of 11 cases associated with hypertension

The term vitamin P encompasses several closely related flavone glucosides derived from plants Various forms of the vitamin have been known as citrin, hesperidin and rutin²¹² Citrin is a crude product containing vitamin C as well as hesperidin and other flavone glucosides Hesperidin and rutin are pure crystalline products The clinical response to vitamin P has been determined by changes in the capillary-fragility test^{211 212} and by clinical improvement The specificity of vitamin P for the treatment of increased capillary-fragility states seems well established by the recurrence of increased capillary fragility when vitamin P therapy is discontinued and subsequent restoration of normal fragility with readministration of the vitamin²¹¹ On the basis of a small number of observations, Shanno²¹² expressed the belief that rutin might be superior to hesperidin

The spectrum of therapeutic indications for vitamin P continues to broaden as an increasing number of clinical observations are published Shanno²¹² found that rutin was of value in preventing vascular accidents in patients with hypertension, maintaining normal capillary fragility in patients being treated with thiocyanate and controlling pulmonary bleeding of an unexplained nature but associated with increased capillary fragility Rutin offers hope of being a specific remedy for the treatment of familial hemorrhagic telangiectasia²¹³

The capillary fragility was improved by doses of vitamin P ranging up to as much as 300 mg per day in two series of diabetic patients who showed diabetic retinopathy, but in neither series was there any evidence that vitamin P improved the pathologic state of the eye grounds^{214 215} On the other hand, MacLean and Brambel²¹⁶ observed 21 patients with vascular retinopathies, other than diabetic, in which rutin and Dicumarol together

anemia, and the necessity for using folic acid in cases of pernicious anemia that are sensitive to liver extract no longer needs to be considered, since the discovery of vitamin B₁₂.

Vitamin B₁₂

After one false stop at folic acid, the twenty-year search for the antipernicious-anemia factor of liver extract appears to have achieved its goal with the discovery of vitamin B₁₂. In 1948 Rickes et al¹⁹⁴ reported the isolation from concentrated liver extracts of minute quantities of a red crystalline material, which Shorbf¹⁹⁶ found to be eleven thousand times more active than potent liver extracts by a bioassay method that appeared to be very specific for the antipernicious-anemia factor. The clinical effectiveness of this crystalline material was demonstrated by West,⁵⁰ who found that 3, 6 and 150 gamma of vitamin B₁₂ produced a positive hematologic response in 3 cases of Addisonian pernicious anemia. The crystals were named vitamin B₁₂ because that term was nonspecific and connoted only nutritional significance.¹⁹⁴ Although the chemical nature of vitamin B₁₂ is still undetermined, further investigation has shown it to be a cobalt complex.¹⁹⁶ This is the first time that cobalt has been shown to be an essential trace element in human nutrition. The red color of the crystals is explained in part at least by their cobalt content. The vitamin is heat stable but is inactivated at room temperature in dilute alkaline or dilute acid solutions.¹⁹⁶

Scarcity of vitamin B₁₂ greatly limited its clinical trial at first. The presence of vitamin B₁₂ activity in many foods led to the search for a more plentiful source of this factor, and *Actinomyces (Streptomyces) griseus* was found to produce a red crystalline substance that had the same physical, biologic and clinical properties as vitamin B₁₂ from liver.¹⁹⁷⁻¹⁹⁸ As a result, crystalline vitamin B₁₂ from *A. griseus* is now readily available and relatively inexpensive.

A rapidly growing number of reports confirm West's original observation of the hematologic effectiveness of intramuscular vitamin B₁₂ in patients with pernicious anemia,¹⁷⁹⁻¹⁹⁹⁻²⁰² and the vitamin produces responses equal to those obtained with liver extract in cases of nutritional macrocytic anemia,¹⁷⁹⁻¹⁹⁹⁻²⁰³ nontropical sprue¹⁷⁹⁻¹⁹⁹ and tropical sprue.²⁰³ Adequate doses of vitamin B₁₂ produce a maximal reticulocyte response in four to nine days²⁰⁰⁻²⁰³ and restoration of the red-cell count, white-cell count and platelets to a normal level in four to eight weeks, but in some cases, Hall and Campbell²⁰⁰ observed that after 8 weeks of therapy with as much as 160 gamma of vitamin B₁₂, the red-cell count reached a plateau at 4,000,000 to 4,500,000. This incomplete response was attributed to either inadequate dosage or the elderly state of the patients. The rapidity with which the bone

marrow changes from a megaloblastic to a normoblastic state is amazing. Within nine hours of the injection of 1 gamma of vitamin B₁₂, definite maturation of the megaloblasts was noted,²⁰⁰ and complete restoration of the bone marrow to a normal state occurred within forty-eight to ninety-six hours.²⁰⁰⁻²⁰² Clinical improvement in cases of pernicious anemia occurred within two to five days of the onset of therapy.²⁰²⁻²⁰³ Patients with tropical sprue showed a decrease in bowel movements and abdominal distention six or seven days after treatment was begun.²⁰³

The inadequacy of folic acid in preventing the development of central-nervous-system complications in patients with Addisonian pernicious anemia led to the postulation of a deficiency of two liver factors in pernicious anemia. One factor was folic acid, which promoted the maturation of erythrocytes, and the other a hypothetical nutrient required for the prevention of neurologic damage. Such a postulation became unnecessary when Berk et al²⁰⁴ found that vitamin B₁₂ caused a marked improvement in the neurologic symptoms that developed in a patient with pernicious anemia who was receiving pteroylglutamic acid. As a result of this observation, later confirmed by others,²⁰¹⁻²⁰³⁻²⁰⁵ Berk and his co-workers²⁰⁶ stated that a deficiency of vitamin B₁₂ may be closely related to the natural origin of both the blood and nervous changes of pernicious anemia. The glossitis of pernicious anemia also responds to vitamin B₁₂,²⁰¹⁻²⁰²⁻²⁰⁵ a fact that adds weight to the belief that vitamin B₁₂ is the antipernicious-anemia factor of liver extract.

A new concept of the pathogenesis of pernicious anemia and of the role of the intrinsic factor has resulted from experiments with oral administration of vitamin B₁₂ to patients with Addisonian pernicious anemia. Berk et al²⁰⁶ found that oral administration of vitamin B₁₂ was ineffective hematopoietically, but when given orally with neutralized gastric juice from a normal person, vitamin B₁₂ elicited a reticulocyte response of as much as 16 per cent with a rise in the red-cell count. A similar observation is reported by Spies and his associates.²⁰³ Fecal analysis for vitamin B₁₂ activity²⁰¹⁻²⁰⁶ showed an excretion of many times the amount of vitamin B₁₂ needed for treatment. These findings suggest that vitamin B₁₂ is closely related to the extrinsic (food) factor and that the purpose of the intrinsic (stomach) factor is to promote absorption of vitamin B₁₂ from the intestinal tract, rather than to react with the extrinsic factor to produce the erythrocyte maturation factor. Consequently, the fundamental defect in Addisonian pernicious anemia may be inadequate intestinal absorption due to a deficiency of intrinsic factor.

Another property of vitamin B₁₂, unrelated to the macrocytic anemias, is an unconfirmed report

polyuria, muscular weakness lassitude and headache. These represent earlier symptoms and are a warning to discontinue the drug.²³¹ More serious results of vitamin D intoxication include metastatic tissue calcification, renal insufficiency and death.²³¹⁻²³³ In general, the toxic symptoms of vitamin D poisoning are associated with a rise in serum calcium but toxic manifestations are also found without any evidence of serum calcium elevation.¹⁴⁷ This suggests that vitamin D itself is toxic aside from its effect upon calcium metabolism. It is safe to assume that any dose greater than 50,000 units per day is potentially dangerous. A high milk consumption may potentiate the toxicity of vitamin D, and the use of vitamin D is contraindicated in cases of arteriosclerosis, hypertension and renal disease.²³²⁻²³⁴ Treatment for vitamin D intoxication includes withdrawal of the medication, elimination of milk from the diet and liberal administration of physiologic saline solution intravenously.²³⁵

As for the other fat-soluble vitamins, large doses of vitamin E caused headaches, dizziness and vertigo¹⁶¹ and such symptoms as a sensation of heat, tingling, headache and tinnitus were temporary ill effects in some patients who received 100 mg of Synkavite or 180 mg of Hvitkinone intravenously.²³⁶

In view of these toxic manifestations although an infrequent occurrence with some of the vitamins, the promiscuous use of massive doses of purified vitamins is not considered justified on the grounds "that they cannot do harm." Another ill effect, although not actually toxicity from the use of large doses of purified vitamins is the appearance of deficiency manifestations that are believed to be on the basis of vitamin imbalance. This subject is discussed further below.

ANTIVITAMINS AND VITAMIN IMBALANCE

As a conclusion to this review of the therapeutic uses of vitamin supplements it is worth while to consider briefly the investigations of antivitamin and vitamin imbalance that may produce a "conditioned" vitamin deficiency.

An antivitamin is defined in an excellent review by Wright⁹ as any substance that interferes with the synthesis or metabolism of a vitamin. This interference may be due to inactivation or destruction of the vitamin or an irreversible combination between the vitamin and the antivitamin. In most cases, however, the antivitamin functions as a competitive inhibitor—that is, it is a substance that is so nearly similar in chemical structure to the vitamin that it can enter into biologic systems in place of the vitamin, but is physiologically inactive. The effect of the vitamin antagonist is dependent upon the ratio of the quantity of the analogue to that of the vitamin.²³⁷ The inhibitory effect of the antivitamin can be abolished

if there is a sufficient supply of the vitamin in question, apparently because there may be a greater natural affinity of the cellular enzyme system for the vitamin.

The original observation that suggested the possibility of antivitamin is the well known antagonism of paraaminobenzoic acid and sulfonamide. It is through the study of bacterial nutrition that many of the vitamin-antivitamin relations have been elucidated. In this way, the search for antivitamin aids in the development of chemotherapeutic compounds. Conversely, antivitamin, by blocking enzyme systems, may be used in establishing the role of various vitamins in metabolism.

In Wright's⁹ review most of the antivitamin mentioned were synthetic products and were primarily research tools.

So far very few antivitamin have been discovered in food, but the demonstration of an anti-niacin compound in corn²³⁸ lends support to the earlier postulation that pellagra was due to the toxic effect of corn and explains why there was an absence of pellagra in persons living on diets that contained much less niacin than those of corn eaters who developed pellagra. The isolation of another natural analogue, the hemorrhagic agent of sweet-clover disease,²³⁹ made it possible to discover vitamin K. Natural antivitamin for thiamine²⁴⁰ and biotin²⁴¹ have been isolated. The antithiamine content of certain raw fish may produce thiamin deficiency in man.²⁴²

More recently certain synthetic antivitamin have offered a ray of hope in the treatment of cancer. The most promising of these to date are the folic acid antagonists, of which the best known is aminopterin.²⁴³

It is theoretically possible for chemotherapeutic agents (antivitamin) to enter into enzyme systems in man and thus to manifest a "conditioned" vitamin deficiency.⁹ Whether antivitamin, through their effect upon intestinal synthesis of vitamins can cause vitamin deficiency in man is open to question, but positive proof of such an effect has not been produced as yet.⁹

The literature on antivitamin is voluminous. In this review discussion is limited to a mere indication of such aspects of antivitamin as are contingent upon the therapeutic use of vitamins.

Attention has been directed occasionally to the concept of vitamin imbalance,²⁴⁴⁻²⁴⁶ a concept that is a strong argument against the use of purified vitamin supplements particularly the members of the vitamin B complex. When pellagrins were given niacin they often showed signs of riboflavin or thiamine deficiency.²⁴⁴⁻²⁴⁶ It was said that niacin "unmasked" the other deficiencies and that most deficiency diseases were multiple. A more probable explanation of this phenomenon is that the use of supplements of niacin increased the

resulted in sufficient improvement to warrant further trial with this type of therapy. Twenty patients with long-standing arthritis who were shown to have increased capillary fragility were studied by Warter et al.²¹⁷ The patients were divided into three groups, one receiving 200 mg of vitamin C alone, a second 200 mg of vitamin P, and the third a combination of 100 mg of vitamin P and 100 mg of vitamin C. The group given vitamin C alone showed no improvement in capillary fragility after four months of therapy. The capillary fragility was improved by the vitamin P in both the other two groups. I can supplement these reports from my own experience with rutin. The daily administration of 60 to 120 mg reduced the bleeding tendency in several patients with liver disease in whom it was previously shown that there was no impairment of the prothrombin function, fibrinogen level or vitamin C status.

Several cases of unexplained bleeding of the gums have been shown to improve and relapse on several occasions as rutin was administered or discontinued.

The minimal requirement for vitamin P has not been determined. In the clinical studies reported above, the dosages have varied from 40 to 300 mg, with an average dosage of 60 to 120 mg per day. No toxic effects have been reported by any investigators, and as much as 15 gm has been given orally without any reaction.²¹⁸ Sulfonamides were shown by Kushlan²¹⁹ to interfere with the efficacy of rutin. As a result, he recommended that, if sulfonamides must be given, the dosage of rutin be doubled or trebled.

TOXICITY OF VITAMINS

Massive supplements of purified vitamins are given too often without concern about any possible toxic effect because it is generally believed that even if the vitamin supplement will do no good, at least it will do no harm. It is fortunate that most vitamins, with the exception of vitamin D, have such a low level of toxicity that the LD₅₀ for animals is in the range of several hundred milligrams per kilogram of body weight. Nevertheless, there are enough scattered reports of toxic manifestations from the use of various vitamins to make one pause before employing the large doses of vitamins that are sometimes given.

It has long been known among Arctic explorers that the ingestion of polar-bear liver will cause a serious illness, and this has been recently explained by demonstration of an excessive vitamin A content of the polar-bear liver. Wolbach²²⁰ studied the effect of excessive amounts of vitamin A upon animals. When 1000 or more international units of vitamin A per gram of body weight was given, absorption of bone occurred, with resulting fractures. There were also weight loss, skin lesions, liver damage due to excessive storing of fat and an increase in the size of the adrenal glands.²²⁰

Several reports of toxic manifestations in human beings have appeared in the literature. In 3 young children who had received doses in excess of 100,000 international units per day over a long period, the outstanding clinical features were anorexia, irritability, bone pain, dry, cracked lips, sparse, coarse hair and hepatomegaly. X-ray studies of the bones showed periosteal proliferation not unlike that seen with scurvy. The children all recovered when vitamin A supplementation was discontinued.^{221, 222} An adult who had taken 6,000,000 units of vitamin A for five successive days was reported to show vertigo, headache, vomiting, excitation and gastric irritability.²²³

The B complex has exhibited relatively few manifestations of toxicity. Among several reports of sudden death following the intravenous injection of thiamine is that of Reingold and Webb,²²⁴ who described a sudden death after the fourth intravenous injection of thiamine that they believed to be due to anaphylaxis. Because of the possibility of sensitivity to thiamine, the intravenous use of this vitamin represents a potential hazard.²²⁵

Powers²²⁶ reported circulatory collapse after the intravenous injection of approximately 30 mg of niacin, and 2 similar cases were described by Pelner.²²⁷ A scaly, follicular dermatitis has been observed to occur during the use of pyridoxine in the treatment of radiation sickness.²²⁸ The dermatitis disappeared upon withdrawal of the vitamin and recurred with resumption of pyridoxine therapy. Para-aminobenzoic acid may cause acidosis, leukopenia and abdominal distention, according to Ravenel.²²⁹ In addition to the leukopenia previously mentioned, Zarafonitis²³⁰ reported such toxic manifestations as drug fever, dermatitis medicamentosa, nausea, vomiting and a fatal case of toxic hepatitis. Transient vertigo, syncope and headache were occasionally observed after the intravenous administration of 150 mg of folic acid, a procedure that has now become obsolete.²³¹ To complete the summary of ill effects from the vitamin B complex, the observation of Alvarez²³² is well worth emphasis—namely, that in some people with unexplained abdominal cramps, the cause will be found to be vitamin capsules and the patients will have relief when the vitamin supplements are discontinued.

To judge from the numerous reports, the toxic manifestations resulting from large doses of vitamin D must be well known. Of all of the vitamins, this is potentially the most toxic, and the enthusiastic reports of benefit, either real or fancied, in the treatment of arthritis and certain skin diseases have led to the ingestion of tremendous quantities of vitamin D. Anning et al.²³³ observed toxic symptoms in 19 per cent of 200 patients who had received daily doses averaging 100,000 to 150,000 units. The symptoms of vitamin D toxicity include anorexia, nausea and vomiting, diarrhea,

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Correction In the Medical Progress report by Dr George W Thorn and his associates entitled "Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease," which appeared in the October 6 issue of the *Journal* the last six words in the final sentence of the first paragraph on page 536 should be changed to read "a finding recently confirmed in further experiments" 26 "

demand for riboflavin or thiamine in a person who was in a borderline state of nutrition with respect to the latter

Animal experimentation has suggested two other mechanisms for the production of "conditioned" vitamin deficiencies by the use of large doses of one or two purified vitamins. Antagonism between members of the vitamin B complex was offered by Richards²⁴⁶ to explain the development of pyridoxine deficiency in rats given large amounts of thiamine. Supplee et al²⁴⁷ demonstrated that administration of thiamine and pantothenic acid caused an increased urinary excretion of riboflavin.

Reports of some clinical evidence of vitamin imbalance have been reviewed by Richards²⁴⁶. A case of ariboflavinosis that developed after lengthy treatment with thiamine is described by Gripwall.⁶ The "burning-feet" syndrome and the leg pains of subjects experimentally deficient in vitamins were made worse when the patients were given purified supplements of the better known members of the vitamin B complex, but were relieved when the patients were fed a luxurious diet or given the whole vitamin B complex in the form of yeast.^{24, 25} I have observed several cases in which glossitis and cheilosis developed while the patients were receiving large doses of thiamine, riboflavin and niacin, and in which "cures" were obtained by discontinuance of the vitamin supplements. Creation of a vitamin imbalance is the probable basis for the ill effect of folic acid on the central nervous system.¹⁸⁵

These observations suggest a need for caution in the use of large doses of purified vitamin supplements, especially in patients who are in a state of subclinical deficiency.

SUMMARY AND CONCLUSIONS

The need for the widespread consumption of purified vitamin supplements is questioned. A critical review of the current vitamin literature shows that the minimal requirements for the vitamins essential to man are much less than the Recommended Dietary Allowances. Vitamin-deficiency states are now infrequent in the United States. The lack of objective evidence of any improvement in health, fitness or work capacity of large population groups who received purified vitamin supplements suggests that the average American diet is adequate enough to prevent subclinical vitamin deficiency. Many of the so-called signs of vitamin deficiency are nonspecific and are not alleviated by vitamin supplementation. The use of vitamins as supportive therapy in infections and chronic diseases is largely empiric. Therefore, there seems to be little need for vitamin supplements from the nutritional standpoint.

Although many claims for the therapeutic value of vitamins in certain pathologic states will not withstand the test of controlled study, there are

some conditions in which a specific vitamin has value by virtue of its pharmacologic properties.

Not only is the administration of large doses of purified vitamins often wasteful and foolish, but also serious consideration must be given to the possibility of a toxic effect or the development of a vitamin imbalance.

If a definite state of avitaminosis exists, long-term use of vitamin supplements is unnecessary. The best suggestion is that of Cowgill to "vitaminize" the patient for a few days with three to five times the requirements and then establish him on a good diet.

In conclusion, I believe that if a person takes a good diet, he will not benefit from vitamin supplements, and that if the patient does not take an adequate diet, the treatment is a good diet, not vitamins.

I am indebted to Miss Kate Spencer, who devoted many long hours to searching through the medical literature for articles on vitamins.

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senting the state of New Hampshire in the National Congress, and that they be urged and respectfully requested to use every effort at their command to prevent the enactment of compulsory health insurance legislation

This motion was duly seconded and was carried. President Dunbar then stated that the Society needed organization, which would cost money. The problem was how to raise that money. Should the Society raise its dues to a certain amount, and fit the services to that amount? Or should it consider the services that it must have and make the dues fit the services?

Next to be considered was the cost of employing the Woodbury firm. Their budget called for \$14,391, but it was possible that some donations might be obtained to cover some of that, which would only make it necessary for the Society to raise \$6,891. Also, the matter of employing a law assistant to the Secretary should be considered. That matter would have to be taken up by the next president and the Committee on Public Relations.

It had been suggested that New Hampshire organize with Vermont and Maine, and it would take time to organize a system of that kind. The cost of such a program could not be estimated.

Dr Bowler moved that the dues be increased to \$40 a year.

The motion was duly seconded.

Dr Bowler then spoke as follows:

It is quite certain that the circle in the budget has to be cut into at some point. The question of the expenditure side of that budget is so undeterminable at the present time that it is impossible to estimate it accurately. The items that we know are the campaign which you heard Dr Dunbar say is in the neighborhood of \$15,000. There may be some offsets or some transfers that can be worked out during the year with other organizations. However, that does not seem to be a good basis for the budget. So that probably, at least at this point, it ought not to be considered as ours.

The next large question is the question of the full-time executive secretary, which was discussed last evening. The possibilities are quite wide and quite unknown or unexplored.

Dr Metcalf has said in his letter that the imposition of the Society on the willingness, charity and energy of one person regarding the work to be done is absurd.

We are in a situation today that is bound to mean more work. Speaking of the load, I hope that Dr Metcalf's letter can be tabled to the point where he will continue until this program is approved and worked out. There are possibilities of a tri-state program, and it might be something that the Society would be interested in.

We have been running on a tin-horn budget, as we all know, for some time, and now we are at the point where we shall have to do one thing or the other.

My motion for the dues of \$40 a year may seem to have been picked out of the air, and it is, to some extent, but if you look at it, it adds up to an income of around \$25,000. But, it is not a lot of money in terms of the items we shall have to account for.

Dr Feiner stated that Dr Dunbar had mentioned that the budget was about \$14,000 for public relations, and any efficient secretary would require a minimum salary of \$4000 or \$5000 a year, which would make a total of \$19,000. He did not know just what the total of paying members was.

Secretary Metcalf replied that it was about 600.

Dr Feiner then observed \$30 per member would be required for that one item of expense. He did not think that even \$35 was sufficient. He did not consider it too much to raise the dues to at least \$45 or even \$50 a year, rather than have to ask for more money again. He therefore moved that Dr Bowler's motion be amended so that the dues would be \$50 a year.

Dr Brown asked how much the American Medical Association would want next year.

Dr D G Smith answered that Dr Lull had said he thought there would be no assessment in 1950. To date, about \$2,000,000 had been collected, and Dr Lull did not believe that there would be an assessment in 1950.

The motion of Dr Bowler that the dues be raised to \$40 was duly seconded and was carried unanimously.

Dr Dye then proposed that the following amendment to Chapter X, Section 1, of the Constitution and By-laws be laid on the table: "An assessment of \$40 per capita on the membership of the component societies is hereby made the annual dues of this society." After further discussion the motion was amended to read "The House of Delegates shall determine the amount of the annual dues." The motion was laid on the table.

Dr Holyoke then spoke as follows:

I was asked by the Society of Clinical Pathologists of the State to present what we know are some of the problems that will come up in connection with blood banking in the State in the near future.

Of course, I think the fact that you passed a resolution last night indicates that you are aware of some of those problems. First of all, I think that we all agree that the establishment of many blood banks throughout the State is certainly advantageous, in that it makes available to the various hospitals a large supply of blood of various types for immediate use, so that anyone can be given a transfusion.

In 1937 the first blood bank was established. The first banks established were purely hospital banks, to supply a given hospital. Since that time literally thousands of banks have been established throughout the United States. The present trend is away from a single hospital bank toward a centralized bank. So that in one city, where there are several hospitals, there will be one bank supplying all the hospitals within the community.

There are actually several possibilities whereby that can be brought about. One hospital in the city may set up a bank and supply all other hospitals with blood, and it will be a co-operative effort.

Another effort, perhaps most widely used throughout the United States is to have the so-called community bank. These banks are usually under the direction of the county medical societies. They supply all the hospitals in a given area with blood.

One other possibility, and the reason why we, in the various county societies in the State, ought to think about the problem, is the establishment of a state-wide Red Cross blood bank. We shall not hear much from the Red Cross for probably a year, because they have their hands full in setting up other banks. But perhaps next year, they will sound out the various county societies and perhaps the state society as to whether it would like to have set up within the State a large blood bank to supply the State with blood.

Their system is to procure the blood and turn it over to the hospitals after it is drawn.

NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-EIGHTH ANNIVERSARY (Concluded)

House of Delegates, June 13, 14 and 15, 1949

Dr Crisp referred to a communication from the president of the New Hampshire Pharmaceutical Association, registering a protest against dispensing of drugs by physicians in groups. This matter had been discussed at the annual meeting of the Association, which also protested against the employment of pharmacists by physicians, private ownership and so forth.

The Secretary stated that his impression was that the druggists objected to the fact that doctors were passing out pills to their patients, and not writing prescriptions.

Dr Crisp replied that the druggists were also against the establishment of dispensing pharmacies employing pharmacists, and run by doctors.

Dr Gifford stated that several pharmacists had informed him that physicians have had their own dispensaries within the particular group, and that the patient must go there to get his medicine.

Dr Bowler said that he assumed that the protest was not aimed at the individual physician dispensing in his own office, which would be ridiculous. His group, however, would be interested in the development by hospitals of their own pharmacies, in the future, perhaps, because that had become an established method for some time.

President Dunbar referred to correspondence with Mr Smith, who was wholeheartedly with the medical profession in its campaign against socialized medicine and who had even sent his personal check as a contribution to the campaign. Dr Dunbar knew of only one clinic in the State that operated a drugstore, in the Winnepesaukee area.

Dr Walck was of the opinion that the medical profession should encourage all possible support from the pharmacists. Mr Smith had been one of the most energetic workers in Strafford County co-operating with the Committee and appeared to be wholeheartedly behind the whole program against socialized medicine.

Dr Jessup stated that the protest appeared to be directed largely against his group. He asked what the basic objection of the pharmacists was, since his group did not dispense but hired two fully qualified pharmacists to do all the work. The group had noted that a large percentage of patients did not use its own pharmacy. Prescriptions that could not be filled in pharmacies within the State were not used. The system had originally been started, in part at least, to facilitate the dispensing of medicines to patients, which all phy-

sicians do to some extent. Originally, it had been meant to be a small drug room, and since there were eleven or twelve doctors in the group, it seemed more to the point to consolidate the drugs in one room, rather than to have twelve dispensaries. It was a regularly chartered drugstore, with its own bookkeeping and is separated from the group. The building was owned by the clinic group.

Secretary Metcalf asked if that was the group in Laconia. Dr Walck replied that it was.

Dr Bowler moved that the protest be referred to the Committee on Public Relations.

This motion was duly seconded and was carried.

President Dunbar moved that the Committee on Public Relations give consideration to the organization of state-wide or local health conferences of doctors, laymen and consumers, similar to the conference held in Massachusetts last February.

This motion was duly seconded and was carried.

President Dunbar also moved that the Society participate in the Conference of Presidents, and that the House ratify the payment of \$10.00 for this purpose.

This motion was duly seconded and was carried.

President Dunbar then moved that the House of Delegates pass a resolution against compulsory health insurance, as follows:

WHEREAS, under a system of free enterprise and personal initiative, the American Medical profession has attained for the people of these United States the highest standards of scientific performance, treatment and research to be found in the world, and

WHEREAS, there exists in many forms voluntary health insurance whereby payments for health care may be effected on a purely voluntary budgetary basis, and

WHEREAS, under voluntary health care programs the people of this country are left free to select their physicians and hospitals and to carry such voluntary health insurance as they may wish, and

WHEREAS, under compulsory health insurance employees, employers and the self-employed, as well as those in other categories, would be faced with a compulsory tax on annual income, earning power or wages to support a governmentally controlled medical program, and

WHEREAS, the experience of all nations where government has assumed control of medical services has shown that there has been a gradual erosion of free enterprise and a progressive deterioration of medical standards and medical care to the detriment of the health of the people,

NOW, THEREFORE, BE IT RESOLVED, that the New Hampshire Medical Society does hereby go on record against any form of compulsory health insurance or any system of politically controlled medicine, firm in its belief that the American tradition of free enterprise may best be carried out by the people and for the people through voluntary means, and that a copy of this resolution be forwarded to the president of the United States and to Senators Styles Bridges and Charles W. Tobey and to Congressmen Chester E. Merrow and Norris Cotton repre-

Secretary Metcalf then pointed out the advantages of having the *New England Journal of Medicine* handle the publication, which was a big job. If the Publication Committee had to take over that work in three months, he would certainly resign from the Committee.

Dr Leonard withdrew the sentence referring to the suggestion of publishing the *Transactions* within three months.

Speaker Dube suggested that the matter be referred to the Publications Committee, of which the Secretary was the chairman.

The Secretary stated that certain portions of the book were valuable. The account of these meetings held in the last three days, the committee reports, the list of members, the obituaries, and other phases might be occasionally used.

Dr Bowler stated that he was in favor of supporting the continuance of the *Transactions*, if only for the historical value, and he moved the question.

Dr Leonard's motion was then read, excluding the suggestion that the transactions be published within three months.

Secretary Metcalf stated the present cost of the books was \$3 a volume, 660 copies had been received this year, at a cost, roughly, of \$2000.

Speaker Dube asked those in favor of the motion to signify assent by raising their right hands.

There were 13 "No" votes, and the motion was lost.

Dr Leonard, in accordance with the suggestion of the Delegate to the American Medical Association, moved that the term of the Delegates of the New Hampshire Medical Society begin on January 1 of the year after his election.

This motion was duly seconded and was carried.

Dr Leonard, also in response to the suggestion of the Delegate to the American Medical Association, moved that the New Hampshire Medical Society co-operate with the American Medical Association by requesting each county society to submit the name of one of its members as the "outstanding general practitioner of the year."

This motion was duly seconded, and was carried.

Dr Leonard, as a delegate from Rockingham County, presented the name of Dr Cleon W Colby for life membership.

This motion was duly seconded and was carried.

The financial report of the Trustees was then presented as follows:

JANUARY 1-DECEMBER 31 1948

GENERAL FUND

<i>Receipts</i>			
Balance on hand January 1 1948		\$2 764 60	
Nashua Trust Company	Int.	11 41	
Portsmouth Tr & Guarantee	Int.	36 44	
New Hampshire Savings	Int.	21 32	
United States Series G Bonds	Int.	100 00	
Total			\$2 933 77
<i>Expenditures</i>			
Cash balance December 31 1948			\$2 933 77
United States Series G Bonds			5 000 00
Total			\$7 933 77

BARTLETT FUND

<i>Receipts</i>			
Balance on hand January 1 1948		\$2 259 75	
Portsmouth Savings Bank	Int.	69 54	
United States Series G Bonds	Int.	75 00	
Cash Balance December 31 1948			2 404 29
United States Series G Bonds			2 000 00
Total			\$4 404 29

PRAY FUND

<i>Receipts</i>			
Balance on hand January 1 1948		\$319 50	
Strafford Savings Bank	Int.	5 50	
United States Series G Bond	Int.	25 00	
Total			349 86
<i>Expenditures</i>			
Essay Prize			0
Cash Balance December 31 1948			349 86
United States Series G Bonds			1 000 00
Total			\$1,349 86

BURNHAM FUND

<i>Receipts</i>			
Balance on hand January 1 1948		\$1 091 81	
New Hampshire Savings Bank	Int.	27 62	
United States Series G Bond	Int.	25 00	
Total			\$1 144 43
<i>Expenditures</i>			
Essay Prize			0
Cash Balance December 31 1948			1 144 43
United States Series G Bonds			1 000 00
Total			\$2 144 43

BENEVOLENCE FUND

<i>Receipts</i>			
Balance on hand January 1 1948		\$3 895 60	
New Hampshire Savings Bank	Int.	98 95	
United States Series G Bonds	Int.	75 00	
Dr. C. R. Metcalf		35 00	
Total Receipts & Cash Balance December 31 1948			4 104 53
United States Series G Bonds			3 000 00
Total			\$7 104 53

Dr George C Wilkins then spoke as follows:

I should like to have the privilege of speaking for the Board of Trustees about the Benevolence Fund, which was started in 1931, and discussed at the meeting Monday afternoon. That fund was started with the idea of building up a fund sufficient to give an income to help out any indigent physician in the Society.

At first, we took \$1 from each person's subscription, and that was allocated to the Fund. That was cut down to fifty cents, and then it was cut down to nothing. We have had no income except from the invested funds and from a very small contribution of \$25 to \$50 from the auxiliaries of three different county societies.

Twice within the last two years, I have been asked if some money was available to help out an indigent physician who has come upon hard times and was unable to do anything about it. However, we cannot use the principal. We only have \$7104 at the present time.

The Trustees would like very much to have the \$1 portion of the dues set aside for the Benevolence Fund, in order to build it up to a point where we could use the income to help someone out.

I think that in line with that, it is worth saying that their system of getting donors has worked very well in some locations. The Red Cross blood banks have been a great asset in some communities, and in others, they have not been so good.

In some places, a great stress is still laid on individual use of the blood, and on being morally bound to replace the blood from friends or members of families. Other banks have gone on the basis that the blood is free, it is yours, and you don't have to do anything about it. But I think the Red Cross banks that have had that system have not been a success.

In the State at present, there are only five banks set up. There are a few others in hospitals, which carry a fair supply of blood on the refrigerator shelves, but, it is not a definite thing, so that it would be conceivable that those hospitals might be short of blood.

Two of the banks in the State do make the blood available at times to doctors in surrounding towns or surrounding communities. But we have virtually no community blood banks at the present time in the State.

There is a Red Cross bank in Massachusetts that is functioning and doing, as far as I can tell, a fairly good job. It ought to do a better job, as time goes on.

In Vermont, within the next three or four months, there will be a blood bank set up under the auspices of the Red Cross. This bank is going to supply eastern New York and all of Vermont, and they are ready — if the members of the various county medical societies in New Hampshire wish them to do so — to supply part of the blood to them.

Also, there is in process the setting up of a blood bank for the city of Portland, Maine.

So that we shall have these large banks all around the perimeter of the State.

As to what the banks can do, I think we could sum it up and say that a large blood bank can ensure the people in the neighborhood of an adequate dose of blood. Certainly, it is an efficient way to obtain blood. It is a method whereby small hospitals and small users of blood can have available to them ample supplies of blood.

There is one thing in line with the national policy. It would have set up through the State a number of large blood banks, whereby we shall be able to help each other in times of disaster. Of course, the national Government is thinking a lot about that at the present time.

One other advantage in having a large blood bank is that it makes available to the doctors or the hospitals that are co-operating with the program plasma products, particularly albumin, that is important because the albumin prepared from plasma is virus free, and there is no need to worry about infectious hepatitis, which is becoming a tremendous problem for people using blood in any volume at all, or using blood products.

If you decide that you would like to co-operate with some of the Red Cross Bank programs, remember that must be done through the counties. Red Cross does not establish it anywhere, unless the county medical societies agree to have it done.

This problem will come up next year so that each county society and the State Society may consider and talk about it at the next meeting.

Upon motion duly made, seconded and voted, the second meeting of the House of Delegates adjourned at 10 30 a m.

The Third Meeting of the House of Delegates was called to order by Speaker Dube at 9 20 a m on June 15, 1949.

The following members responded to roll call.

The President, *ex-officio*
 The Vice-President, *ex-officio*
 The Secretary-Treasurer, *ex-officio*
 James Jessup, alternate for Roger Brassard, Laconia
 Samuel Feiner, Ashland
 W J Paul Dye, Wolfeboro
 Howard Sawyer, alternate for Francis J C Dube
 Marjorie A Parsons, Colebrook
 William H Gifford, Colebrook
 Leslie K Sycamore, Hanover
 Reginald K House, Hanover

Norman W Crisp, Nashua
 Harris E Powers, Manchester
 James B Woodman, Franklin
 Francis Brown, alternate for Warren H. Butterfield
 Ellsworth Tracy, alternate for William D Penhale
 Donald W Leonard, Exeter
 Fred Fernald, Nottingham
 Edna Walck, Dover
 Albert E Barcomb, Rochester
 B Read Lewin, Claremont
 Addison Roe, Newport

Dr Dye moved that Section 1 of Chapter X of the By-laws, which is headed "Assessments and Expenditures," be amended to read as follows: "The House of Delegates shall determine the dues of members of this Society."

This motion was duly seconded and was carried.

Dr Bowler then moved that the dues of the New Hampshire Medical Society be \$40.

This motion was duly seconded and was carried.

Dr Leonard, for the Committee on Officers' Reports, moved that the custom of sending delegates from the New Hampshire Medical Society to the annual meetings of the other New England state societies be renewed.

This motion was duly seconded and was carried.

In accordance with the suggestion in the report of the Secretary, he then moved that the Committee on Amendments to the Constitution and By-laws be instructed to prepare an up-to-date copy of the entire Constitution and By-laws, and that the Secretary be authorized to incorporate them in a printed booklet for the reference of the members.

This motion was duly seconded.

Dr Bowler offered an amendment that, on review and before printing, the copy be submitted to the next House of Delegates.

Dr Leonard accepted the amendment.

Upon a voice vote, the motion was carried.

Dr Leonard, for the Committee on Officers' Reports, moved that the *Transactions* be printed in an annual volume, omitting reprints of scientific and other papers presented at the annual meeting, except such essays as are awarded prizes by the Society and any other papers having specific application to the Society. It was also suggested in this motion that publication of the *Transactions* be made within three months of the annual meeting.

Secretary Metcalf remarked that the papers that go into the *Transactions* are printed previously in the *New England Journal of Medicine*, being spread out over a whole year. The papers are kept set up in print and simply transferred to the *Transactions*. In that way, the Society saved about a thousand dollars. If a volume was brought out in three months, the material would have to be specially set, at a cost of \$6 apiece.

Dr Leonard stated that the motion was to omit the scientific papers from the *Transactions*, except the prize essays and those of merit.

Dr Bowler then moved that the continuance of Mr Woodbury's services be approved, pending the report of the Budget Committee

This motion was duly seconded and was carried

Dr Feiner recommended that at the next year's meeting, the House of Delegate's meetings be started on a Sunday, so that the bulk of the

business could be finished before the scientific sessions began

Dr Dye moved that the House adjourn

This motion was duly seconded and was carried

Whereupon, the third meeting of the House of Delegates was adjourned at 11 o'clock in the forenoon

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35521

PRESENTATION OF CASE

A sixty-two-year-old woman was admitted to the hospital for the fourth time with a complaint of coma following epileptic seizures

The patient had had recurrent epileptic seizures for about fifteen years. These attacks were variable in frequency, duration and nature, and recurred at any time of day or night. In some of them she was able to carry out co-ordinated motor activity in an automatic way for a few minutes to an hour or more while seemingly "in a daze." In others, she suddenly lost consciousness without warning and fell to the ground, where she lay motionless for a few minutes, sometimes with urinary incontinence. Rarely, there were tonic-clonic convulsions, with tongue biting. Some of the attacks were heralded by peculiar unlocalized "crawling" sensations in various parts of her body, often in the back of her neck. In all of them, there was total amnesia for the attack itself. These attacks occurred anywhere from once in two or three months to three or four times a week. Over the course of the years, she received many forms of anticonvulsant medication, which never controlled her seizures satisfactorily. Repeated electroencephalograms showed diffuse abnormalities consistent with epilepsy. Radiograms were normal except for osteoporosis of the left posterior clinoid process. Lumbar punctures were normal, and the neurologic findings were negative. During the six months before

admission, in addition to her previous attacks, she began having more frequent episodes of unresponsiveness and unconsciousness between meals, lasting up to three hours at a time, during which she was sometimes noisy and restless. They became progressively more severe and occurred at least three times daily, always occurring between meals or between supper and bedtime.

Physical examination revealed an obese woman, who was dazed and confused. There were a number of cutaneous scars from previous injuries and burns. The remainder of the physical examination and the neurologic examination were negative.

The temperature was 99°F, the pulse 82, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 12 gm and a white-cell count of 14,670, with a normal differential. Urinalysis was normal. A fasting blood sugar was 47 mg per 100 cc, a repeat test on the following day was 35 mg per 100 cc. The nonprotein nitrogen was 21 mg, the calcium 9.4 mg, and the potassium 4.6 mg per 100 cc. The sodium was 141 milliequiv, and the chloride 105 milliequiv per liter. The carbon dioxide was 29.4 milliequiv per liter. A cephalin-flocculation test was negative in twenty-four and forty-eight hours. The total protein was 6.49 gm per 100 cc, with 4.43 gm of albumin and 2.06 gm of globulin. The bromsulphalein test showed 16 per cent retention of the dye. The phosphorus was 3.7 mg per 100 cc. A blood Hinton test was negative.

A glucose tolerance test revealed a high value of 208 mg per 100 cc in two hours and a low value of 58 mg in six hours. The response of the patient, with a fasting blood sugar of 47 mg per 100 cc, to an injection of 0.01 cc of epinephrine (in a dilution of 1:1000) per kilogram of body weight was 54 mg per 100 cc in fifteen minutes and 39 mg in sixty minutes.

The patient was fasted for twenty-four hours, at which time a convulsion occurred. A blood sugar determination at this time was 45 mg per 100 cc. She responded immediately to intravenous glucose therapy.

Two weeks after admission an operation was performed.

These cases do not come up very often, but when they do, it is rather a sad position for us to be in, to say that we cannot do anything to help them. Therefore, the Trustees would like very much to have that allocation made to the Benevolence Fund, if the House of Delegates believes that it should be done.

Dr Bowler moved that the question be referred to the budget committee for next year.

Speaker Dube stated that there was no budget committee.

Dr Bowler replied that, temporarily, the officers could be used as such. They would look over the budget, on the basis of the new dues, the campaign work, the question of the new executive secretary and so forth.

Secretary Metcalf remarked that the Trustees were responsible for the invested funds, and that the Treasurer acted as a budget committee, paying out the necessary expenses. The present rule was that nobody could spend any money unless the House gave its approval, so that the budget committee would be purely advisory.

Dr Bowler stated that the budget had to be set up. He assumed that a special meeting of the House would be called as early as these things were in shape to be recommended, meanwhile, work must be done.

Dr Feiner asked if it had to be a standing committee. If not, the by-laws would not have to be changed, because a special committee could be appointed by the Chairman, to report back at the next meeting of the House of Delegates.

Dr Bowler stated that at present there was no budget committee as an officers' committee. But, in the meantime, he supposed that the matter had to be handled by the officers in this preliminary work with the budget.

Dr Wilkins remarked that the request of the Trustees could only be granted by a vote of the House of Delegates.

Dr Crisp asked how much was needed to put the fund in working order.

Dr Wilkins replied that, originally, the plan had been that after the fund had reached \$10,000 the income could be used for any such purpose, and if the income from the fund was not used, it could be added to the principal. Of course the income from \$10,000 was not too much, and it would not go very far, but the fund should be that amount before any of the interest was taken away.

Dr Bowler re-phrased his motion to state that this item be referred to a committee to be appointed by the President, to be considered along with a study of the budget, the recommendations to be reported to the next meeting of the House of Delegates, and that Dr Wilkins's recommendation be referred to this Committee.

This motion was duly seconded and was carried.

President Dunbar then moved that the House of Delegates go on record as being in sympathy with the objectives of the American Diabetes Association,

— that is, to improve the treatment of diabetes, to bring the newest knowledge of the disease to all physicians, to encourage and support research in the field and to increase knowledge of diabetes among the general public, — that the incoming president appoint a diabetes committee of three to aid in this program and, that the Secretary inform the county societies of this action, recommending that each appoint a diabetes committee.

This motion was duly seconded and was carried.

Dr Sycamore moved that a vote of appreciation be extended to Dr Dunbar for the time and effort that he had put into the service of the Society during this past year, and for the inspiring leadership he had given.

This motion was duly seconded and was carried.

Dr Sycamore then made a similar motion with reference to the Secretary-Treasurer.

This motion was duly seconded and was carried.

Speaker Dube stated that the next item of business was the selection of a place for the next annual meeting.

Dr Bowler stated that he had been asked a year ago whether Hanover would be interested in having the Society next year. This would not be practical because of the so-called Hanover Holiday, which is the week between commencement and reunion. However, he suggested that Hanover be considered for the following year. He moved that Newcastle be chosen for 1950.

Dr Dye seconded the motion.

Dr Gifford suggested the Mount Washington Hotel, which had adequate floor space for the exhibits. This might inconvenience the physicians in the cities, who like to be able to dash in and see their patients and dash back to the meetings and catch a lecture or see what is going on.

Dr Barcomb seconded Dr Gifford's suggestion.

Dr Dye stated that the exhibits brought in a certain amount of income, and the Mount Washington Hotel had stated that they would be delighted to have the Society meet there, and also that they had adequate space and facilities for all the exhibits.

Speaker Dube stated the motion that the Society meet at the Wentworth Hotel in Newcastle next year.

Dr Dye seconded a motion by Dr Bowler that the members be polled by postal card, and amended that motion so that the officers of the Society would be empowered to act with reference to the final selection of the site.

Dr Bowler accepted the amendment.

Speaker Dube stated the motion before the House that the Secretary poll the Society, and that the officers be empowered to act upon the result of the poll, to select the future place of meeting next year. He asked all those in favor of this motion to signify assent by saying "aye."

There was a chorus of "ayes," with one dissenting "no," and the motion was carried.

method of determining blood insulin. In the case under discussion it would be most helpful in eliminating an erroneous diagnosis that could arise from misinterpretation of spells that seem to have been epileptic or neurotic.

DR ROBERT S SCHWAB: This electroencephalogram was taken before the operation and shows marked abnormalities that are underlined with pencil (Fig 1). We have evidence of localization in the right temporal region because of the large spikes

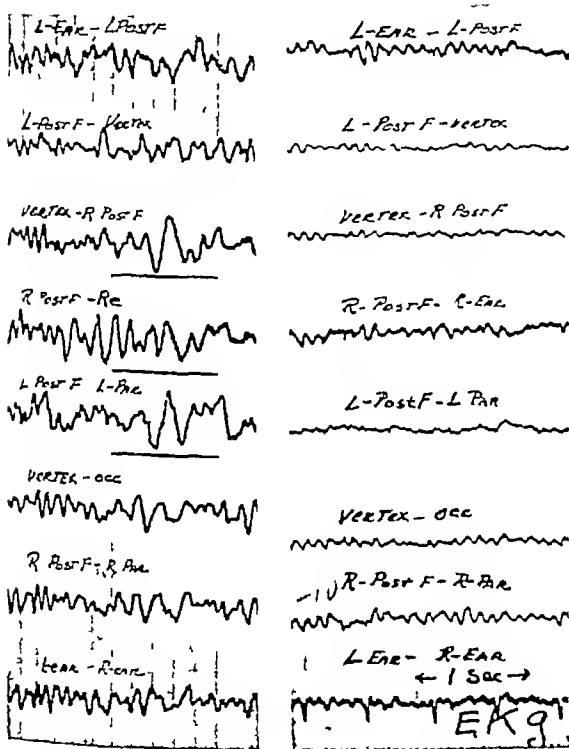


FIGURE 1

FIGURE 2

in the basal lead. Here is a normal electroencephalogram for comparison (Fig 2).

CLINICAL DIAGNOSIS

Islet-cell adenoma of pancreas

DR CHAPMAN'S DIAGNOSIS

Islet-cell adenoma of pancreas

ANATOMICAL DIAGNOSES

Islet-cell adenoma of pancreas

Epilepsy

Carcinoma of thyroid gland

PATHOLOGICAL DISCUSSION

DR OLIVER COPE: We reached the same diagnosis that Dr Chapman did and, accordingly,

opened the abdomen and looked at the pancreas. It was large and lobular, and no definite tumor was seen or felt. It looked a little bit larger than the normal pancreas. The woman was very obese, and the pancreas felt big and fat. I excised the tail and body of the pancreas down to the neck, leaving head and neck. After excision we incised the specimen longitudinally, starting at the tail and cutting into each lobule as we slit it down. There was one little lobule in the mid-body that looked like the rest but that, when cut into, proved to be a little adenoma. I had taken out more than was needed. The tumor was characteristic; it was the size of a small, seedless green grape, not as big as 2 cm in diameter. It was well circumscribed and of firm whitish tissue.

My face was scarlet red about this patient. She had been cared for by the Burn Service during the war, and we, like the neurologists, had failed to make the diagnosis. She had made many trips to this hospital; many electroencephalograms had been done, and she had seen many doctors. It was not until Dr Balboni saw her at home in an attack that suspicion was aroused as to what was wrong. He thought it was not an ordinary seizure and sent her in with the diagnosis of hyperinsulinism and said, "Please determine the blood sugar." He was convinced about the diagnosis. The patient was sent home, however, without a blood sugar determination, and two days later he sent her back and said, "Please do a blood sugar determination" (I do not think he said "please" the second time). What interested me was that many had seen this patient, and many noted that she suffered from a state of confusion, and yet the attack was never classified until Dr Balboni looked at the patient and said, "This is not an ordinary epileptiform seizure."

DR SCHWAB: The postoperative electroencephalogram was exactly the same as the preoperative. I would like to ask Dr Chapman how he explains the persistence of epileptic waves after removal of an islet-cell adenoma of the pancreas.

DR CHAPMAN: That is interesting because I think it happened in a patient who had, perhaps, a fundamental underlying disorder in the brain that was activated by hypoglycemia. It fits with Romano's patient who had fundamental personality changes that were not altered after removal of his adenoma. However, he stopped having the epileptic attacks after operation.

DR SCHWAB: Would the original disease be the cause of the seizures indirectly? People who have hypoglycemia usually do not have convulsions, but they do faint and fall and such falls may damage the brain and produce scars. The scars then cause the seizures. I do not know whether we have an answer to this speculation.

DR BENJAMIN CASTLEMAN: Following operation she had more attacks. She had one on the ninth postoperative day and one on the tenth.

DIFFERENTIAL DIAGNOSIS

DR EARLE M CHAPMAN* It seems clear from the history and data presented that this patient suffered from hypoglycemia. That is a positive clinical diagnosis.

What are the main causes of hypoglycemia? There may be four main causes, and it is for us to go through them to determine which seems most likely to fit this patient. First, I think we have to consider abnormality of the liver cells. If a failure of gluconeogenesis in the liver takes place, hypoglycemia can occur. Did this patient have enough evidence to support a diagnosis of severe liver disease to explain this syndrome? When a normal liver is removed profound hypoglycemia may result, but 80 per cent must be removed before hypoglycemia is produced. So I cannot believe that the evidence here indicates that 80 per cent of this patient's liver was impaired. All the liver-function studies were normal, with the single exception of 16 per cent retention of bromsulfalein. I am inclined to discount this as one of the minor variations in laboratory data that tend to confuse one.

Secondly, I think a decreased gluconeogenesis can result from diminishing output of anterior pituitary hormone, thyroid hormone or cortical or medullary secretions of the adrenal gland. On review of the data, there is no evidence on which I can base a diagnosis of endocrine disease of the pituitary, thyroid or adrenal glands. It is true that the basal metabolic rate is not reported. It is likewise true that x-ray examination disclosed some osteoporosis of the posterior clinoid process. I will have to depend on Dr Wyman to tell me whether he thinks there is a significant abnormality in the region of the pituitary body.

DR STANLEY M WYMAN I do not believe that the skull films are definitely abnormal for a person of this age. Osteoporosis of the posterior clinoids seems to be rather general, and there is no evidence of erosion and no evidence of increase in size of the sella turcica. Otherwise, the bones of the skull appear within normal limits. I should be inclined to discount the reported osteoporosis of the clinoids. There are other films available that you may like to see. The films of the chest are grossly unsatisfactory, they are examinations of a heavy person taken with a portable machine. They do show tortuosity of the aorta but no other definitely localized intrinsic disease. In the one film of the abdomen the liver shadow appears to be within normal limits in size and shape. The kidneys are well seen and appear normal, the left lies lower than usual. There are no masses above it, however.

DR CHAPMAN I will accept your word that there is little or no evidence for pituitary disease in the x-ray films.

A third cause of hypoglycemia is that produced by long-endured or violent exercise. Occasionally, severe and prolonged exercise will produce hypoglycemia. I have seen one such case in a young boy who did very hard work over a long period and had a fainting spell in which we established the diagnosis of hypoglycemia and he recovered immediately. I would like to read from an article by Romano¹ that bears on this point of attacks of low blood sugar occurring after violent exertion.

The day following the New England hurricane in September, 1938, he engaged in a kind of wood-chopping contest with a number of neighbors who were clearing fallen timber from their property. After some fifteen minutes of vigorous chopping, he suddenly clutched his axe menacingly, and with a dazed and glassy-eyed expression, wandered about the neighborhood, terrifying people. He was again taken to the Peter Bent Brigham Hospital, where house officers were struck by his confusion, mumbling speech and constant grotesque, ataxic and purposeless movements. Convinced of the hysterical character of his disorder, house officers sprayed a fine stream of ethyl chloride on his bare abdomen to startle him out of his attack. He appeared to respond promptly to this interesting therapy, for he came to himself immediately. He professed amnesia for the entire episode, and the diagnosis of hysteria seemed definitely confirmed. (The probable effectiveness of a large glass of ginger ale, which the patient had been persuaded to drink just before the ethyl chloride treatment, was not appreciated.)

This patient was subsequently proved to have periodic hypoglycemia.

This leads me to the fourth possibility and the one that probably explains this patient's condition which was followed for over fifteen years in our Out Patient Department—the inhibitory action of insulin on the gluconeogenesis of the liver itself, in other words, hyperinsulinism. The history is typical of hyperinsulinism. The data of low blood sugar and response to epinephrine are characteristic, and, in the end, an operation was performed. My guess is that the abdomen was explored and that possibly an islet-cell tumor of the pancreas was discovered and if an enlarged pancreas was found, a subtotal resection was performed. I remember a case in Baltimore seen by Dr Edward Jarrett, in which an extremely large pancreas was discovered, and the surgeon held it up and said "How much will we take off?" And he said "Oh, about there," and they chopped it off about "there," and the patient had no more attacks. No islet-cell tumor was discovered in that case. It would be helpful if they discovered a tumor in the case under discussion.

There are four types of islet cells, and the beta cells that occupy the periphery are smaller than the others and are considered the producers of antidiabetic hormones.

This case illustrates another point to me the need of a method to determine the level of blood insulin. When I visited the Banting Institute last spring, I was impressed with the amount of intensive work going on in this problem. Dr Best is devoting a good share of his efforts in working out a practical

*Associate physician Massachusetts General Hospital

lymphedema" was made, she returned to her physician. At this time she was receiving codeine because of the pain. She stated that the swelling decreased when she stayed in bed, and that during her last two menstrual periods the pain and swelling were aggravated. Rectal examination revealed an increase in size of the fixed pelvic mass.

The menstrual history was negative, her periods occurring every twenty-six to twenty-eight days, lasting four days and without pain. She had a history of four miscarriages at two to four months during the past eight years.

At the age of eighteen, six months following an appendectomy, a "tumor of the abdominal wall" was excised. At that time she was told by the surgeon that she would probably be unable to have children.

Physical examination revealed a well developed and well nourished woman. In the mid thigh the right leg measured 54 cm, and the left 45 cm, at the calf the right was 42 cm, and the left 34 cm. The right ankle measured 28 cm, and the left 24.8 cm. On pelvic examination a hard, tender mass was felt high in the pelvis. The rest of the examination was negative.

The blood pressure was 130 systolic, 80 diastolic.

Examination of the blood and urine was negative. A prothrombin time was 22 seconds (normal, 18 seconds). An x-ray film of the chest was normal.

On the day following admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR IRAD B. HARDY*: We have here the problem of moderately advanced unilateral lymphedema coming on rather rapidly in a young woman. Of course, we must decide what the pelvic mass was and whether it had any causal relation to the swelling. In the first place, I think we can very quickly rule out the systemic causes of swelling of the legs simply on the basis that this was a unilateral affair and such conditions as nutritional edema, renal disease, heart disease and hyperthyroidism can be discarded. Also, among the mechanical causes of edema any lesion above the bifurcation of the iliacs can be ruled out because this was a unilateral process.

I suspect all we have in the way of x-ray studies is a chest film. May we see it?

DR STANLEY WYMAN: I do not believe there is anything to add to the record, Dr Hardy. It appears to be within normal limits.

DR HARDY: No intravenous pyelogram?

DR WYMAN: No.

DR HARDY: To review the protocol, there are some things we might point out briefly. For several years this woman had mild swelling in both ankles by the end of the day. I do not believe that is very

significant, it is a very common complaint. I doubt if it had much bearing on this particular case.

Ten months before being seen in the hospital she began to have some cramps in her leg and later in her thigh, and finally she noted that the leg was red and that a red line had appeared on the inner aspect of the thigh. There was no mention of any special degree of swelling, and I presume there was none. This may have represented an initial episode of mild cellulitis, possibly the red streak was lymphangitis or superficial thrombophlebitis. At any rate, this redness and streaking were not mentioned again, and I think we can assume, if it was an initial episode of cellulitis and infection, that at least it was not repeated over the following months. Several months later (we do not know how much later or how soon before she came in) she had swelling in the groin, and we again have to assume that the swelling had become progressive. She also had an irregular, firm, fixed pelvic mass.

She was then lost track of and upon returning to her physician, which was just about the time she entered the hospital, she had been taking codeine for the relief of pain, which had apparently developed somewhere along the line. I think that, although swollen legs are certainly uncomfortable, the necessity for codeine is not very common. The usual therapy to relieve the pain associated with simple lymphedema is aspirin, an elastic support or elevation. I suspect that this necessity for codeine may indicate that there was some process going on that was involving the nerves as well as the lymphatic drainage.

We then find that the menstrual cycle was essentially normal but that she had had over a period of eight years several miscarriages in the early months. I wonder whether that means a mechanical obstruction in the pelvis, which prevented full-term pregnancies. However, I am of the opinion that that was not the case and that there was probably a hormonal imbalance that prevented her from going on to full term. Later, the mass in the pelvis was apparently of fairly rapid development and probably did not account for the fact that she had not been able to have full-term pregnancies for as far back as eight years previously.

On admission to the hospital the physical examination, such as we have to go on, shows that she had a moderately diffuse swelling located in the right groin. There is no mention of any marked venous stasis, and no mention of a great deal of induration, pigmentation or dilated veins to suggest a postphlebotic state. There is no mention of any redness or cellulitis, which we would have expected to be present if she had had an inflammatory process going on all this time. Since it is not mentioned, I shall assume that it had not been present. No palpable lymph nodes are recorded.

*Assistant in surgery, Massachusetts General Hospital.

DR CHAPMAN And so she had two diseases

DR COPE That is the question that Dr Schwab brings up whether or not one disease gave rise to another

DR CASTLEMAN At autopsy

DR CHAPMAN At autopsy¹ I thought they cured her

DR CASTLEMAN We were kind enough not to inform you of that

She was operated on in April of this year and just died a few months ago. We were unable to find anything grossly in the brain to account for the epileptic attacks. On the other hand, we did find something more. She had a large thyroid tumor that was very hard, measured about 10 by 8 by 4 cm and extended down into the mediastinum to about 3 cm above the arch of the aorta. She was very obese, and that is probably why the tumor could not be felt. Microscopically it was a very anaplastic tumor with giant cells and in places looked like a fibrosarcoma. It is the type of malignant lesion that is often called carcinosarcoma—a lesion that is probably primarily epithelial. It had metastasized to the lungs but not to any of the regional lymph nodes.

DR COPE I think that I am right in saying that she suffered respiratory distress for forty-eight hours before death and died at home. The respiratory distress was of short duration.

DR CHAPMAN Death came rapidly, in other words

DR SCHWAB Is there any microscopical report of the temporal region of the brain?

DR CASTLEMAN Yes, but the findings did not differ from other regions of the cerebral cortex. According to Dr Kubik, there was an increase in astrocytes in the deeper layers of the cortex and in scattered areas in the white matter, but these findings were probably of recent origin. I am afraid we did not disclose any focus to explain the seizures.

DR SCHWAB One would not expect the sections to show much unless the dura was involved under the temporal lobe, was there any pigmentation there?

DR CASTLEMAN No

DR SCHWAB I would like to comment briefly on the low blood sugar. It does not produce convulsions. It has to be at extremely low levels to produce convulsions with a normal brain. Insulin has recently been tried in the diagnosis of epilepsy. Some people have seizures at a level of 30 mg and others, at a level of 60 mg per 100 cc. That is a differential method of diagnosing epilepsy but not a general rule. The low blood sugar does not produce convulsions in normal people.

DR CHAPMAN With apologies to the Peter Bent Brigham Hospital, I should relate the following. In 1930 a patient had severe hypoglycemia. She fell, fractured her arm, and came to our Emergency Ward. The fracture was treated and, later,

she had another seizure and still another seizure, and finally at the Brigham Hospital, Dr Pokorny made the proper diagnosis of hypoglycemia. She was explored, and the islet-cell tumor removed. This is the first case of this disorder reported in New England.²

DR CASTLEMAN In the case under discussion, after the tumor was removed, the blood sugar ranged between 150 and 200 mg per 100 cc, always above 100 mg, whereas previously it was around 45 mg.

A PHYSICIAN What did the pancreas show at autopsy?

DR CASTLEMAN It was perfectly normal. There was no increase in the number of islets in the remainder of the pancreas either at operation or at autopsy.

DR SCHWAB Does this disturbance in the thyroid function intensify the effect of islet-cell tumor in reducing blood sugar?

DR CHAPMAN In general, when there is more thyroid hormone, the diabetes is worse.

DR COPE It is possible that the thyroid lesion was not palpable at the time of operation on the pancreas, it was rapidly growing and presumably developed within a relatively short time. This poor woman was plagued by both these diseases. I think the thyroid carcinoma was probably not related to the other two.

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CASE 35522

PRESENTATION OF CASE

A thirty-eight-year-old married office worker entered the hospital with a complaint of swelling of the right leg.

For the past several years she had experienced mild swelling of both ankles at the end of the day, more marked after being on her feet for long hours. Ten months prior to admission she began to experience cramps in her right foot at night, apparently waking her and subsiding in five or ten minutes. No change in appearance of the extremity was noted at this time, but later the cramps recurred higher in the leg, the leg became red, and a red "line" appeared on the inner aspect of the thigh. Several months following this episode she was seen in a physician's office. At that time swelling of the right leg was as high as the groin. Pelvic examination revealed a firm, fixed, irregular mass, high on the right in the region of the uterosacral ligament. About five months later, after visiting at least one hospital, where a diagnosis of "idiopathic

PATHOLOGICAL DISCUSSION

DR ULFELDER Dr Hardy was quite correct in classifying this as a case of noninflammatory secondary, unilateral lymphedema because that is exactly what she had. She had occlusion of the right external iliac vein by a very firm and fibrous mass intimately connected with the lymph nodes in this area. The only unusual feature of the case and in my experience it is unique, was the nature of the disease within and outside the lymph nodes, because this was also endometriosis. She had endometriosis of the lymph nodes in the operative area surrounding the external iliac vein. Endometriosis was also present outside the lymph nodes and at the time of operation it was very easily demonstrable that this was the cause of the difficulty. The peritoneum was opened on this side, and dissection carried down along the vessels. The external iliac artery was adherent posteriorly to it but was not involved in the pathologic process. The ureter was not involved in the disease process. It could easily be separated from the peritoneum but the external iliac vein on the right side was completely surrounded by the diseased tissue and was in turn adherent to the pelvic wall. I was not able, of course, to dissect this out because it was too fixed a process, but I was able to free the vein from the pelvic wall and I obtained a biopsy of the fibrous tissue along the pelvic wall. I was also able to remove a number of lymph nodes in the immediate vicinity. The pelvic tumor was entirely separate. It was an endometrioma of the rectovaginal pouch in the usual position behind the cervical segment and with the bowel adherent to it.

DR ALFRED KRAVES Was not the absence of dysmenorrhea quite unusual?

DR ULFELDER Dysmenorrhea is classically the symptom of endometriosis, particularly increasing dysmenorrhea. On the other hand, in any analysis of series of cases in which this diagnosis has been made histologically it is usually noted that about 40 to 50 per cent of patients have not had pelvic pain, it is not by any means a *sine qua non*.

DR MALLORY I have a slide I would like to demonstrate. This is from one of the lymph nodes in the region of the iliac vein and here one can quite clearly see a gland lined with columnar epithelium. Around it is hemorrhagic stroma of the endometrial type. This gland lies just at the margin of the node and is a very clear-cut focus of endometriosis within the node strongly suggestive of a metastasis. I believe metastasis does occur in this condition infrequently but not extremely rarely. There was recently reported from the Gynecological Clinic at Cornell a series of 5 cases showing metastases of endometriosis to lymph nodes and various places around the pelvis.²

There was only one lead in the story as written, and that was the accentuation of symptoms at the time of the menstrual periods. That is a rather flimsy lead I grant, because so many women have accentuation of every kind of symptom at that time.

DR KRAVES Was she relieved of her edema?

DR ULFELDER It is not fair to judge so soon. She was operated on recently and of course her rest in bed brought about a marked decrease in the edema.

DR MALLORY In handling this case you thought that it was necessary to remove both ovaries?

DR ULFELDER Yes I did, for two reasons. I could not tell grossly that this was endometriosis, although that was my impression, it has never been described as producing this picture. So from a diagnostic point of view, I thought I was dealing with a malignant lesion, with metastasis to that site, or with endometriosis, either one of which in this situation would have demanded removal of all the pelvic organs, including both ovaries.

DR MALLORY One can be quite sure that after sterilization, it would not progress, but one cannot be sure how much the fibrosis will regress.

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In deciding just what type of lymphedema we are dealing with I will run through very briefly one of the better classifications of lymphedema that might be able to help us. I have picked Dr. E. V. Allen's¹ classification, because I think it is the best and easiest to fit into this picture. He divides unilateral lymphedema into noninflammatory and inflammatory groups. Under the noninflammatory group we have the primary and secondary cases. In the primary cases, we have what he calls lymphedema praecox — lymphedema of unknown etiology that comes on in adolescence, usually in females. There is no known obstruction. The lymph vessels are just not capable of handling things, and a gradual process of fibrosis and further obstruction and swelling develops. There is usually no story of cellulitis or recurrent sepsis to account for it. In addition to the praecox type, there is a congenital type of primary lymphedema. But we can rule that out because this occurred in her thirty-eighth year and there was no previous sign, except a little bit of swelling, which I do not believe was true lymphedema.

Under the secondary type of noninflammatory lymphedema, we have occlusion of the lymph system by malignant growth such as metastatic involvement of lymph nodes, or following eradication of the lymph nodes, such as we frequently see after a radical axillary or groin dissection. The cases that follow x-ray or radium treatments are also in this group.

The second division is the inflammatory group of lymphedema, and here also there are infections in the leg brought on for no apparent cause, there being no obvious focus of entry. The episodes are initiated by chills and fever and other symptoms that we have not seen in this case, and therefore I assume that it does not fit into that group.

In the secondary type of inflammatory lymphedema are the cases associated with venous stasis due to old phlebitis and those in which there is marked venous insufficiency and obvious routes of entry for secondary sepsis. The fungous infections and filariasis are considered to be of this group. Also, there are the cases of lymphedema following severe local injury and trauma.

In reviewing all the groups under the classification, I believe this woman of thirty-eight with rapidly increasing swelling in whom there was no evidence of recurrent chills or fever, no significant findings to suggest venous disease or fungous infection and no local injury, probably fits into the secondary group of noninflammatory cases. There may have been occlusion of the lymph channels and lymph nodes in the pelvis and iliac region that was due probably to some type of malignant tumor. We cannot rule out inflammatory disease itself, but I would think if a lesion of this sort were purely inflammatory and widespread enough to cause that

amount of swelling there would have been more reaction such as chills and fever.

From the beginning, it has been my impression that this mass was some kind of retroperitoneal condition rather than a pelvic lesion. The examiners were apparently able to outline a normal ovary, a normal uterus and this mass. The retroperitoneal location does not eliminate an ovarian tumor because the ovary may have been in ectopic position or may have become adherent so that the tumor would invade in that direction and plug the lymphatics, it is very farfetched reasoning. I wonder why the doctor at the time of her second operation, when she was eighteen years old, told her that she would have no children after he had operated on the tumor of the abdominal wall. It is just possible that she had an ovary in the inguinal canal.

Another condition that I have to mention, in spite of the negative abdominal examination, the absence of lymph nodes and the normal chest film, is a localized lymphosarcoma involving the pelvic iliac nodes and causing obstruction to the lymph outflow. Although there were several years between, she had had a considerable amount of surgery, some of it rather extensive, and she could have had interference with lymph structures from postoperative scar formation. This may not have manifested itself for several years. Another possibility is some type of local tumor of the lymph vessels such as lymphangioma. However, I think I will have to say that she probably had a lymphosarcoma of the iliac lymph nodes with obstruction to account for the lymphedema.

DR. TRACY B. MALLORY: Are there any questions or suggestions? Dr. Ulfelder, do you want to tell us the opinion on the wards?

DR. HOWARD ULFELDER: The protocol could not make it as obvious as it was to us who saw the patient that this pelvic mass was very suggestive of endometriosis. It lay in the posterior cul-de-sac as far as we could tell and could be easily palpated both by pelvic and by rectal examination, and on combined examination it seemed to lie against the posterior aspect of the cervix and anterior to the rectum. It was my impression on the basis of this examination that this mass was more likely to be endometriosis in the region of the uterosacral ligaments than anything else.

CLINICAL DIAGNOSIS

Endometriosis

DR. HARDY'S DIAGNOSES

Lymphosarcoma of iliac nodes
Lymphedema

ANATOMICAL DIAGNOSES

Endometriosis of pelvis and retroperitoneal tissues
Endometrial metastasis to iliac lymph node

the world requires time in which to accept a more dynamic philosophy of service and to alter its course accordingly. Being human, it has made its mistake., being decently human, it is willing to acknowledge them and try to mend its ways.

It must always be remembered, however, by those who clamor for action, that many of the problems of health and disease and the proper distribution of medical care are quite insoluble until patient study, day by day and month by month and year by year gradually reveals some of the answers. Even the Alexanders of bureaucracy cannot dissolve these knotty problems simply by cutting them.

So far the best answer to the distribution of medical service appears to lie in the voluntary health insurance plans and the education of the public in the tremendous difficulties, responsibilities and often disappointments, as well as the great achievements, day in and day out, that attend the practice of medicine. These difficulties the doctors themselves are constantly trying to overcome, and are even taxing their own incomes to help in the attempt.

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OLD FARMER'S ALMANAC

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It is the homely traditions of New England, of which the *Almanac* is a tough and persistent symbol, that bind these states together as by a blood relationship. Its fisheries, its forests and its ship-building contributed to the early development of New England and its superb waterpower made it one of the important industrial sections of the country but it was the New England farm that gave New England its characteristic atmosphere.

The rugged, all-purpose New England farm, where the sheep's noses had sometimes to be trimmed down on a grindstone before they could get the grass between the boulders, represented not a cash business but a way of life. It was a way of life filled with hard work, but also with certain amenities, the recollection of which has been preserved by John Greenleaf Whittier, a New England farm boy, and by Robert Frost. It was a way of life that is responsible for a nostalgic sympathy with what *The Old Farmer's Almanac* represents, and for an independence of mind and an individual endurance that make New England still a stronghold of democracy and free enterprise.

"BUT FEAR ITSELF"

THE reassurance once issued to the American people by their president that they had nothing to fear "but fear itself" would not suit every occasion, appropriate as it might have been at that time. There are reasonable fears and unreasonable fears, healthy fears and unhealthy ones.

It is with the latter that Terhune* is concerned in discussing his experiences with a group of patients suffering from the "phobic syndrome." This group, comprising 86 persons, represented 25 per cent of his psychoneurotic patients. Women in the group outnumbered the men two to one. They were mostly under forty years of age and though

*Terhune, W. B. Phobic syndrome: study of eighty-six patients with phobic reactions. *Arch. Neurol. & Psychiat.* 62:162-172, 1949.

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WISE MEN BEARING GIFTS

THE House of Delegates of the American Medical Association, thereby incurring the disapproval of the *Boston Herald* as expressed editorially on December 11, has voted to levy annual dues of \$25 on its members. This new source of revenue, provided for in the by-laws, will supplement the now inadequate income that the Association receives from its publications, and will be used to defray the expenses of its various activities in the interest of better medical care for all.

It would appear that the establishment of these dues is part of the legitimate internal affairs of the Association. When acceptable evidence is brought to light that funds are being improperly or even unwisely used, then it may be hoped that such a friend of the ethical profession of medicine as the *Boston Herald* has been will not withhold its criticism.

To those who are interested in examining all sides of a controversial matter, the constructive activities of the American Medical Association must soon become apparent. Its influence in establishing high standards of medical education and hospital service is a matter of history, and its efforts at maintaining these standards through the Council on Medical Education and Hospitals are part of the record. The Council on Pharmacy and Chemistry is tireless in its positive opposition to "fraud, undesirable secrecy, and objectionable advertising in connection with proprietary medicines." Were the newspapers of the country as truly interested in protecting the health of the public as many of them profess to be, they might have consulted the Council on Pharmacy and Chemistry before accepting some of the full-page advertisements of wonder-working drugs that have recently been flung before the public as an open invitation to self-dosing with insufficiently tested remedies.

The representatives of the Fourth Estate, with conspicuously few exceptions, have done well in holding up the hands of the medical profession, represented by the American Medical Association, in its efforts to protect the public health and its own autonomy by combating compulsory health insurance. Many of the Association's friends, however, and all of its enemies, need to know more about its positive and constructive activities.

In addition to the two mentioned above, they need to know about the councils on scientific assembly, foods and nutrition, physical medicine, medical service, industrial health and national emergency medical service. They need to know about the committees on therapeutic trials and scientific research and on rural medical service, the bureaus of medical economic research and health education that the Association maintains.

With a full knowledge of these and many other activities, they will then be in a better position to weigh the charge of "accenting the negative" that has been expressed or implied so frequently in recent months.

Great bodies move slowly, and the American Medical Association, representing the rank and file of one of the most conservative professions in

the world, requires time in which to accept a more dynamic philosophy of service and to alter its course accordingly. Being human, it has made its mistakes, being decently human, it is willing to acknowledge them and try to mend its ways.

It must always be remembered, however, by those who clamor for action, that many of the problems of health and disease and the proper distribution of medical care are quite insoluble until patient study, day by day and month by month and year by year, gradually reveals some of the answers. Even the Alexanders of bureaucracy cannot dissolve these knotty problems simply by cutting them.

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an eagerly expectant populace on January 2, 1849, and that January 2, 1950, will be a very cold day, that in the middle of the month the danger of chimney fires is imminent and that on January 24, to be marked by a thaw in 1950, the Chilean earthquake occurred in 1939.

It is the homely traditions of New England, of which the *Almanac* is a tough and persistent symbol, that bind these states together as by a blood relationship. Its fisheries, its forests and its ship-building contributed to the early development of New England, and its superb waterpower made it one of the important industrial sections of the country, but it was the New England farm that gave New England its characteristic atmosphere.

The rugged, all-purpose New England farm, where the sheep's noses had sometimes to be trimmed down on a grindstone before they could get the grass between the boulders, represented not a cash business but a way of life. It was a way of life filled with hard work, but also with certain amenities, the recollection of which has been preserved by John Greenleaf Whittier, a New England farm boy, and by Robert Frost. It was a way of life that is responsible for a nostalgic sympathy with what *The Old Farmer's Almanac* represents, and for an independence of mind and an individual endurance that make New England still a stronghold of democracy and free enterprise.

"BUT FEAR ITSELF"

THE reassurance once issued to the American people by their president that they had nothing to fear "but fear itself" would not suit every occasion, appropriate as it might have been at that time. There are reasonable fears and unreasonable fears, healthy fears and unhealthy ones.

It is with the latter that Terhune* is concerned in discussing his experiences with a group of patients suffering from the "phobic syndrome." This group, comprising 86 persons, represented 25 per cent of his psychoneurotic patients. Women in the group outnumbered the men two to one. They were mostly under forty years of age and though

*Terhune W. B. Phobic syndrome: study of eighty-six patients with phobic reactions. *Arch. Neurol. & Psychiat.* 62:162-172, 1949.

outstandingly intelligent and from financially secure families were only moderately successful, chiefly because handicapped by fear

These patients were, on the whole, anxious, dependent, emotionally immature young adults who were trying to realize their ambitions and become self-reliant, successful members of society. They were physically healthy, though soft. Reassuring and of prognostic importance is the fact that none of the 86 ever acquired a psychosis. They did have, however, cyclothymic tendencies and "hyperactive vegetative nervous systems that cause unpleasant symptoms which they do not understand and which then give rise to further fear." They were suggestible, imaginative, sensitive persons, with considerable drive, high standards of conduct, active intelligence and ambition. Fearful of situations that might bring on unconquerable panics within them, their instinct for escape was strong. As the author astutely puts it, "They refuse to enter any place from which they cannot escape quickly and with dignity."

A person with a strongly developed anxiety reaction betraying itself in phobic form may be pitiable indeed. He will not or cannot attend parties or enter any public place. Fearing the somatic avalanche of "faintness, weakness, fatigue, palpitation, perspiration, nausea, tremor and difficulty in breathing" that overwhelms him when he finds himself conspicuous in his inadequacy, he dreads equally the crowded theater and the quiet, but peopled church, the city sidewalk whose crowds he has to face alone and the lonely country road that aggravates his sense of insecurity. He fears the high bridge, the water-girt island and the tunnel, from which there seem to be no escape.

It is not difficult to understand that emotional immaturity must be the basis of such unreasoning phobia—that the phobic person, finding himself unable to cope with the apparently dangerous realities of existence, suffers frustrations, becomes "unfavorably conditioned to specific situations," and retreats to a childish level of adjustment. Consciously he may realize that "there is nothing to fear but fear itself," but what a devastating fear that may become!

The phobic patients representing only 25 per cent of the psychoneurotic persons that Terhune has encountered, emphasize by their relative small numbers the varieties of adjustments that human kind must make, the majority of the having as their basis immaturity of emotional development. Few people there must be, indeed, who regularly enjoy complete emotional maturity. With or without specific phobias, emotional immaturity must account for a great deal of the failure and unhappiness in the world, particularly in environments so complicated that full maturity almost indispensable if they are to be coped with successfully.

The hopeful part of Terhune's paper deals with the apparent success that has rewarded the treatment of the phobias by giving the patient an understanding of his difficulties, socializing him, building up his confidence in himself and reconditioning his fears. By these processes 67 per cent of the group have been permanently relieved of their apprehensions, 24 per cent have been greatly improved to the point where they can work and live efficiently, and only 9 per cent have shown little or no improvement.

Most effective and most efficient of the conditioning mechanisms, however, must be the prevention of these personality disorders. The present road and the road ahead are too rough to be trodden barefoot. If the world's children are to overcome the difficulties that the world presents, they must be conditioned to them from the start.

DR FISHBEIN RETIRES

THE resignation of Dr Morris Fishbein as editor of the *Journal of the American Medical Association* after his service of twenty-five years in that capacity has been accepted by the board of trustees.

During much of this period Dr Fishbein has been a prominent figure on the American scene, considered by many as the standard-bearer of organized medicine. Physically and intellectually tireless, Dr Fishbein early assumed an unofficial leadership in the affairs of the Association that was apparently unchallenged until recent years.

As he leaves the headquarters of the Association, possibly with his energetic tongue held temporarily in his cheek, there remain behind him unquestioned monuments to his vigor and sagacity — the *Journal* and the other publications of the American Medical Association and the real contributions that he has made toward raising the standards of medical practice.

Mr Davis, the man of revelations, is said to be preparing an extraordinary work on medicine, the result of recent interviews with Galen! He was in Boston last week, but whether he met with Galen or Hippocrates here, has not been divulged

Boston M & S J, December 26, 1849

Fourth-year students in approved medical schools are reminded of the *Journal's* prize essay competition on "Recent Advances in the Recognition, Treatment and Control of Poliomyelitis"

For further information see *The New England Journal of Medicine*, September 29, 1949, p 506, or write to the editor

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1949

RÉSUMÉ

DISEASES	NOVEMBER 1949	NOVEMBER 1948	SEVEN-YEAR MEDIAN
Chancroid	4	5	2*
Chicken pox	927	1740	969
Diphtheria	22	37	28
Dog bite	751	789	620
Dysentery bacillary	8	5	21
German measles	33	59	60
Gonorrhea	206	262	378
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	1	15
Malaria	1	1	691
Measles	141	2790	2
Meningitis meningococcal	3	2	5
Meningitis Pfeiffer-bacillus	4	4	4
Meningitis pneumococcal	2	0	0
Meningitis staphylococcal	1	0	0
Meningitis streptococcal	1	0	3
Meningitis undetermined	10	3	523
Mumps	585	1021	24
Poliomyelitis	76	5	7
Salmonellosis	3	5	466
Scarlet fever	236	465	391
Syphilis	133	185	220
Tuberculosis pulmonary	196	232	12
Tuberculosis other forms	7	18	1
Typhoid fever	3	1	4
Undulant fever	1	2	598
Whooping cough	539	254	

*Five-year median.

COMMENT

This month dog bite, poliomyelitis and typhoid fever were above the seven-year median. Diseases below the seven-year median were German measles, measles, mumps and scarlet fever. There were 751 cases of dog bite this month, which was 10% below the 789 cases of November, 1948, when there were 789 cases

Poliomyelitis continued to decline steadily from the high level of August, with 76 cases this month compared to a seven-year median of 24 cases

Scarlet fever was at the lowest incidence ever recorded in November. Measles was at the lowest since 1907, and German measles at the lowest in ten years

The incidence of whooping cough is rising, being at the highest level since December, 1947

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Ayr, 1, Boston, 12, Leominster, 1, Malden, 1, Somerville, 6, Wilmington, 1, total, 22

Dysentery, bacillary, was reported from Boston, 4, Brookline, 1, Cambridge, 1, Somerville, 1, Worcester, 1, total, 8

Encephalitis, infectious, was reported from Lynn, 1, Mansfield, 1, Palmer, 1, Springfield, 1, total, 4

Infectious hepatitis was reported from Revere, 1, total, 1

Malaria was reported from Northampton, 1, total, 1

Meningitis, meningococcal, was reported from Boston, 1, Salem, 1, Springfield, 1, total, 3

Meningitis, Pfeiffer-bacillus, was reported from Belmont, 1, Brockton, 2, Hovoke, 1, total, 4

Meningitis, pneumococcal, was reported from Needham, 1, Worcester, 1, total, 2

Meningitis, streptococcal, was reported from Ashland, 1, total, 1

Meningitis, undetermined, was reported from Danvers, 1, Fall River, 2, Greenfield, 1, Longmeadow, 1, Lowell, 1, Needham, 1, South Hadley, 1, Spencer, 1, Woburn, 1, total, 10

Poliomyelitis was reported from Ashburnham, 1, Attleboro, 1, Boston, 7, Bourne, 1, Brookline, 1, Cambridge, 3, Chelmsford, 2, Concord, 3, Dedham, 1, Dracut, 2, Fitchburg, 1, Greenfield, 1, Hamilton, 1, Hingham, 1, Holliston, 1, Hopedale, 1, Lee, 1, Lexington, 1, Lincoln, 1, Longmeadow, 1, Lowell, 4, Marion, 1, Marshfield, 1, Medford, 2, Milton, 1, Nahant, 1, Nauck, 1, Needham, 1, New Bedford, 1, Newton, 2, North Attleboro, 1, Norwell, 1, Oakham, 1, Orange, 1, Palmer, 1, Pittsfield, 1, Quincy, 1, Saugus, 1, Somerset, 1, Taunton, 1, Tyngsboro, 1, Waltham, 6, Wellesley, 1, Weston, 1, West Springfield, 1, Winchester, 1, Worcester, 6, Wrentham, 1, Plymouth, 1, total, 76

Salmonellosis was reported from Cambridge, 1, Fall River, 1, Norwood, 1, total, 3

Septic sore throat was reported from Boston, 2, Braintree, 1, Fall River, 1, Worcester, 1, total, 5

Tetanus was reported from Gloucester, 1, Pittsfield, 1, total, 2

Typhoid fever was reported from Brookline, 1, Ipswich, 1, Plymouth, 1, total, 3

Undulant fever was reported from North Adams, 1, total, 1

CORRESPONDENCE

LAISSEZ FAIRE

To the Editor Although inactivated myself from the practice of medicine and conscious of a consequent inability to sense the emotions of the man who is in active practice, I feel moved to protest these twenty-five dollar assessments, which seem on the way to becoming a permanent medical liability.

In making this protest may I state that I have no sympathy for the compulsory insurance program but I should like to observe that opposition to the program and contributions to make this opposition effective are by no means the exclusive responsibility of physicians. Physicians will be hurt no more than the average citizen. There is nothing to indicate that a physician's income will be seriously less than at present though his satisfactions and his morale stand to be lowered through loss of incentive. There is reason to predict a dismal future for scientific achievement in the field of medicine. The results of these changes will be felt by the average citizen in higher taxes and a distinct loss in the standards of individual consideration that he now expects from his physician.

Now that the A M A has spent its millions in its educational campaign this year, making these facts clear to the nation, if the majority still wish to have Government hand-

outs, Government bankruptcy and socialized medicine — if they wish to have a look at the inside of a bog — I say, "Let 'em."

I am willing to contribute to a campaign waged by people of all trades and professions but I will not willingly contribute to a fund raised solely by physicians.

ALLAN R. CUNNINGHAM, M.D.

Winchester, Massachusetts

BOOK REVIEWS

Practical Lessons in Psychiatry, By Joseph L. Fetterman, M.D. 8°, cloth, 342 pp., Springfield, Illinois: Charles C. Thomas, 1949. \$5.75.

The author, who has been an executive officer of the School of Military Neuropsychiatry, wrote this book as an outgrowth of lectures at this school and of seminars given in Cleveland. A wealth of material is presented in concentrated form, arising from the author's military and civilian experience. The level, style, together with the very numerous examples, makes this book pleasant reading.

In the introductory chapter on the patient and his personality the author shows that learning never should exclude common sense. Psychoneuroses and their treatment are given rather thorough consideration. The possibilities of "short psychotherapy" are discussed and illustrated by histories. The author expresses his opinion concerning disputed questions and attempts to formulate new interpretations. For instance, he emphasizes the organic factors in the etiology of endogenous depression, and in schizophrenia he adds to the usual types the subdivision of schizoaffective disorders. This last group runs a cyclic course and responds well to shock therapy. The author states, "Those cases which fail to respond and ultimately require confinement to state hospitals are usually true Schizophrenias." The book deals thoroughly with insulin and "electro-coma therapy," which are best suited to the affective disorders. His own working hypothesis is that the mood is cyclic and tends to return to the baseline of average normality. This tendency is also present in manic-depressive states in which the cycle may take a year or more. Electrocoma therapy accelerates this tendency to return to the average state. "The passage of the current through the brain and the convulsion effect the physiological change which proves to be both a stimulus to improve bodily function and a removal of self-attacking mechanisms!" In schizophrenia "this restoration of the mood towards normal may carry with it a change in ideation."

The book deals with all manifestations of mental disorders, and much consideration is given to the military, industrial, legal and social aspects. Dr. Fetterman says in the preface that he planned this book for general practitioners, nurses, psychologists, personnel advisers and social workers, but, the psychiatrist, too, will appreciate many of the opinions, which are borne out by the author's great experience.

Pathology and Surgery of Thyroid Disease. By Joseph L. DeCoursey, M.D., and Cornelius B. DeCoursey, M.D. 8°, cloth, 476 pp., with 93 illustrations. Springfield, Illinois: Charles C. Thomas, 1949. \$10.00.

Recent developments in the treatment of thyroid disease have been unusual. The utilization of ever-increasing varieties of antithyroid drugs and of radioactive iodine in the study and treatment of certain affections of the thyroid gland has been responsible, in a measure, for the publication of several new textbooks relating to the general subject of thyroid disease. This volume brings still another shade of opinion to bear on this, as ever, controversial subject.

These authors, in presenting their convictions in this regard, draw heavily upon their large personal experience in the surgical treatment of thyroid disease. These convictions, in the main, are conventional, and are attested to by the cumulative experience of other recognized ones in the field.

This treatise, consisting of 476 pages with is divided into sixteen chapters. The deal with the anatomy, embryology, physiology of the thyroid gland are adequate in terms of accuracy. The description of the clinical various diseases of the thyroid gland

certain aspects, however, the position of the authors is more novel, and therefore will be subjected to some question in quarters having a comparably large experience with the management of thyroid disease.

It is essentially in the field of therapy that significant differences in points of view will be manifest.

The authors apparently consider iodine (Lugol's solution) as the treatment of choice in the preoperative preparation of the average thyrotoxic patient for thyroidectomy, although they cover, with ample discussion and thorough documentation, the historical development and clinical application of the various thiourea derivatives in the preoperative management of thyrotoxic patients. The authors utilize certain thiourea drugs in conjunction with iodine in the preparation of selected patients with diffuse toxic goiter for thyroidectomy. They state specifically (p. 214), however, that "toxic nodular goiter should not be treated with thiouracil, but should (also) be removed surgically." It is not entirely clear to the reviewer whether the authors mean to say that patients with toxic nodular goiters should not be given thiouracil even as a preliminary adjunct to subsequent thyroidectomy or whether they are merely opposed to its utilization as a substitute for surgery. In the opinion of the reviewer, based upon the experience of the Lahey Clinic, propylthiouracil is currently the preparation of choice in the preliminary restoration of normal metabolism in the presence of either diffuse or nodular toxic goiter. Iodine in the form of Lugol's solution, is employed during the last two or three weeks of thiouracil therapy to induce involution of the hyperplastic gland in the patient with primary hyperthyroidism (diffuse toxic goiter). No iodine is used routinely in the nodular toxic goiters.

The reviewer is in thorough agreement with the authors in their convictions regarding the necessity of treating patients with diffuse and nodular toxic goiters by subtotal thyroidectomy and the importance of iodine in conjunction with thiourea derivatives in the preparation of patients with diffuse toxic goiter (primary hyperthyroidism) for surgery, and is in opposition to the thesis that radioactive iodine will replace surgery in the treatment of thyrotoxicosis.

DeCoursey and DeCoursey advocate routinely the use of small doses of thyroid extract postoperatively for a period of approximately a year in all cases of hyperthyroidism. They base this advocacy on the theory that "by keeping sufficient thyroid in the blood stream following operation, the thyroid remains at rest." They believe that their low incidence of recurrent hyperthyroidism is due, in some measure, to this practice. Some surgeons and internists, with wide experience in the treatment of thyroid disease, will question the validity of this contention, and will believe that the authors' low rate of recurrent hyperthyroidism following subtotal thyroidectomy is probably due to the thoroughness with which the operation is performed. Many will fear the routine use of thyroid extract after operation because of the conviction that, in certain cases, thyrotoxicosis apparently has been induced by its injudicious administration. One might also point out the theoretical possibility that the concentration of iodine in thyroid extract could be responsible for any therapeutic benefit that might derive from the administration of desiccated thyroid in this connection.

In performing thyroidectomy, the authors do not routinely divide the strap muscles, expose the recurrent laryngeal nerve, demonstrate the parathyroid glands or ligate the inferior thyroid artery — technical considerations that are believed to add to the safety of the operation.

This book is well organized, generously illustrated and carefully documented. To this increasingly controversial field of medical and surgical therapy it brings considerable support to certain conventional concepts, and novel convictions in some regards, which may tend to widen the area of conflicting opinion.

Cardiovascular Disease: Fundamentals, differential diagnosis, prognosis and treatment. By Louis H. Sigler, M.D. 8°, cloth, 51 pp., with 149 illustrations. New York: Grune and Stratton, 1949. \$10.00.

Recent, refresher courses for physicians are in the of practically every teaching institution. Here at would serve well as a refresher course in cardiovascular diseases. It covers briefly the fundamentals, differential diagnosis and prognosis. Another

valuable point is the view of the author, who looks upon the heart as a unit affecting the entire organism even though limited clinically to localized structures and organs.

The book covers practically the entire field of cardiology. It starts with a chapter on the general incidence of cardiovascular disease and runs through the whole gamut including congenital heart disease and psychosomatic cardiovascular abnormalities and contains a final chapter on surgery and cardiovascular disease. This book also has a number of very informative illustrations and is well documented. There is, however, one fundamental fault in some places the author is too brief and important other subjects are completely omitted. For example, electrocardiography, which is essential in heart disease, is covered in only one paragraph—making a reference to an article that covers the subject. At least one chapter should have been devoted to this subject. The reviewer found it a very profitable book that briefly covers most of the essentials in the field of cardiology.

BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

From Thirty Years with Freud. By Theodor Reik. Translated by Richard Winston. Second printing. 8°, cloth, 244 pp. New York: International Universities Press, Incorporated, 1949. \$3.75.

This volume is a second printing of a book first published in 1940. The material is divided into four parts: Freud and his followers, including biographic material on Freud; a well-known lecture of Freud's, Freud as a critic of culture; and essays on diverse subjects. To those not owning the 1940 original this reprint presents the opportunity of purchasing this work on psychoanalysis.

Conference on Metabolic Aspects of Corpulence. Transactions of the Sixteenth Meeting, New York, New York, October 21-25, 1947. 8°, cloth, 168 pp., with 39 illustrations. \$3.00. *Transactions of the Seventeenth Meeting, New York, New York, March 29-30, 1948*. 8°, cloth, 246 pp., with 79 illustrations. \$4.00. Edited by Edward C. Reifenstein, Jr., M.D. New York: Josiah Macy, Jr., Foundation, 1948.

In both these conferences a number of papers were presented on the adrenocorticotrophic hormone and adrenal conditions and on protein metabolism. Detailed tables of contents take the place of indexes. The volumes should be in all medical libraries and available to all research workers in the field of metabolism.

Obesity. By Edward H. Ryncarson, M.D., Division of Medicine, Mayo Clinic, and associate professor of medicine, Mayo Foundation and Clifford F. Gastineau, M.D., fellow in medicine, Mayo Foundation, Rochester, Minnesota. 8°, cloth, 134 pp., with 9 illustrations and 16 tables. Springfield, Illinois: Charles C. Thomas, 1949. \$3.50.

This monograph, prepared for the practicing physician, considers the various aspects of obesity. The introduction presents valuable weight tables for men and women of ages twenty-five and over, percentage of overweight and underweight, deaths per 100,000 from all causes and all ages by weight classes, influence of overweight on mortality in persons aged forty-five to fifty years, and the influence of body weight on mortality. In order the physiology, etiology, contraindications to reduction and treatment including diet, psychotherapy, drugs, heat, and exercise and massage are discussed. The chapter on diets was written by Alice Karelake Irmisch and contains many diet tables. There is a bibliography of 422 easily obtainable references. Surprisingly there is not an index. The book should be in all medical libraries and should prove useful to the practicing physician.

Facts About the Course of Life. By E. C. Hamblen, M.D., professor of physiology and associate professor of obstetrics and gynecology, Duke University School of Medicine.

and chief of the endocrine division and endocrinologist, Duke Hospital, Durham, North Carolina. 12°, cloth, 86 pp. Springfield, Illinois: Charles C. Thomas, 1949. \$2.50.

This small book is written for women and presents in simple language the information that they need concerning the menopause, with the object of dispelling unnecessary fears during this period. The anatomy and physiology of the female sexual organs and the endocrine system, hygiene and the nervous and mental conditions incident to this period are discussed. There is a chapter on cancer in which the author points out that the occurrence of cancer during the menopause is chronologic and casual.

Applied Psychoanalysis. Selected objectives of psychotherapy. By Felix Deutsch, M.D. 12°, cloth, 244 pp. New York: Grune & Stratton, 1949. \$3.75.

The Boston Psychoanalytic Society, during the years 1942-1947, conducted a psychiatric clinic for the treatment of neuroses. The knowledge gained during this period is summarized in this small volume. The material is divided into four parts: goal-limited adjustment (sector therapy, with an analysis of two cases, one with fourteen interviews), psychiatry and social work (including psychoanalysis), mental health in industry—job phobia, and family disruption (separation neurosis). A short bibliography is appended to the chapter on mental health in industry. There is a good index. The small volume is well published.

Problems of Early Infancy. Transactions of the Second Conference, March 1-2, 1948, New York, New York. With Supplement: Opening Special Meeting, July 18-19, 1947, New York, New York. Edited by Milton J. E. Senn, M.D., departments of pediatrics and psychiatry, Yale University School of Medicine. 8°, cloth, 120 pp. New York: Josiah Macy, Jr., Foundation, 1948. \$1.00.

The main themes of this conference were the psychological problems of pregnancy and neurotic conditions in children in war. Eighteen persons delivered papers at the meeting. The volume should be in all medical libraries, as well as all the libraries sponsored by the Macy Foundation.

Help Your Eyes. Better Sight. By Margaret D. Corbett, M.D. 8°, cloth, 21 pp. New York: Prentice-Hall, Incorporated, 1949. \$2.50.

In this volume, written for the laity, the author describes the Bates method of relaxation for rebuilding vision in defective eyes.

Outliving Your Years. By Clarence W. Lieb, M.A., M.D. 12°, cloth, 278 pp. New York: Prentice-Hall, Incorporated, 1949. \$2.75.

This popular book, written for persons in their fifties and over, discusses hygiene, work, exercise, hobbies, and the so-called diseases of old age, including heart disease, high blood pressure and cancer. It is pointed out that cancer is not part of the aging process but is prevalent in women of forty to sixty and in men over sixty. Also, the painful condition of arthritis is considered. The text is well written in a simple manner and abounds with common-sense advice.

Public Health Statistics. By Marguerite F. Hall, M.A., Ph.D., associate professor of public-health statistics, School of Public Health, University of Michigan. Second edition, revised. 8°, cloth, 441 pp., with 41 illustrations. New York: Paul B. Hoeber, Incorporated, 1949. \$7.50.

In this revision of a special work, part of the text has been rewritten and the material brought up to date. The statistical tables have been revised, and some tables have been added. There is a new chapter, illustrating three of the most useful applications of life-table techniques to the materials available in public-health activities. A section has been added to the chapter on correlation to give greater emphasis to correlation technique. Likewise, the author has attempted to simplify the basic theory of the application of the normal curve to statistical processing of public-health data. Much of the material in the original chapter on estimates of popula-

tion has been deleted as obsolete because of the new techniques originating with World War II. The section on sampling emphasizes three variables that must be known before the size of the sample can be determined. The publishing is excellent. The book should be in all large public libraries and in all collections on public health and statistics.

Textbook of Medicine. By various authors. Edited by Sir John Conybeare, K B E., M C., D M. (Oxon), F R C P., physician to Guy's Hospital, London. Ninth edition. 8°, cloth, 875 pp., with 28 illustrations. Baltimore: Williams and Wilkins Company, 1949. \$8.00.

This composite textbook, the work of eighteen British physicians, was first published in 1929. Its long life is good evidence of its soundness and popularity. The volume is well published. The paper, type and printing are excellent. There is a good index. The printing was done in Great Britain. The work should be in all the large medical libraries.

The American Nurses Dictionary. The definition & pronunciation of terms in the nursing vocabulary. By Alice L. Price, B S., R N., instructor of nursing arts at Columbia Hospital, Milwaukee 12°, cloth, 656 pp. Philadelphia: W B Saunders Company, 1949. \$3.75.

This new dictionary defines approximately 25,000 words and indicates their pronunciation, a very valuable feature. The text is concluded with a number of tables, including abbreviations, prefixes and suffixes, chemical symbols and elements. The book is well published and should prove generally valuable. It should be in all public and medical libraries.

Vocabulary Guide. A teacher's supplement to the American Nurses Dictionary. 8°, cloth, 101 pp. Philadelphia: W B Saunders Company, 1949.

The separate supplement is designed for nurses and is arranged topically.

NOTICES

SPRINGFIELD HOSPITAL CONFERENCES

The following conferences will be held at the Springfield Hospital, Springfield, Massachusetts, during January, 1950:

Saturday, January 7, 12 noon: Symposium on Diseases of the Thyroid Gland.

I. Diagnosis and Treatment of Simple Goiter and Inflammatory Diseases of the Thyroid Gland (Staff Conference Room).

Saturday, January 14, 12 noon: Symposium on Diseases of the Thyroid Gland.

II. Diagnosis and Treatment of Graves's Disease (Staff Conference Room).

Tuesday, January 17, 8:30 p.m.: Clinical Pathological Conference (Staff Conference Room).

Saturday, January 21, at 11:00 a.m.: Springfield Hospital Guest Speaker Conference. Dr. Samuel Levine, Boston.

Topic: "Auscultation of the Heart."

Saturday, January 28, 12 noon: Symposium on Diseases of the Thyroid Gland.

III. a. Diagnosis and Treatment of Thyroid Neoplasms.

b. Complications following Therapy of Thyroid Disease.

Conferences are open to all interested physicians.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society (formerly the New England Heart Association) will be held in the amphitheater of the Dowling Building, Boston City Hospital, on Monday, January 9, at 8:00 p.m., Dr. Laurence B. Ellis presiding.

PROGRAM

The Use of an Oral Mercurial Diuretic in Ambulatory Patients. Drs. Elliot Bresnick, Johns Abramson and Peter L. Safra.

Khellin in the Treatment of Angina Pectoris. Drs. Harold Osher and Kermit H. Katz.

The Effect of Intravenous Digoxin on the Dynamics of the Circulation in Congestive Heart Failure. Drs. Richard A. Bloomfield, Garth A. Graham, Henry Kraus and Paul H. Pfeiffer.

The Effect of Digitalis on the Oxygen Consumption, Ventilation and Pulse Rate during Exercise in Normal Subjects and Patients with Heart Disease. Drs. Herbert S. Sise and Kenneth Chesky.

Evaluation of Surgical Treatment of Angina Pectoris. Drs. Dwight E. Harken, Robert C. Farrand and Leona R. Norman.

The Use of Cation-Exchange Resins in Patients with Cardiac Edema. A preliminary report. Dr. Henry Kraus.

Interested physicians and medical students are cordially invited to attend.

AMERICAN COLLEGE OF ALLERGISTS

The sixth annual congress of the American College of Allergists will be held at the New Hotel Jefferson, St. Louis, Missouri, January 15 through 18. The subjects of allergy of the eye, dangers of cosmetics, snake venom in the treatment of urticaria, shortening the treatment of hay fever, allergy in France, England and Ireland, relation of allergy to character problems in children, marital adjustments in parents of allergic children and many others will be discussed. Dr. Paul Kallos, of Helsingborg, Sweden, will be awarded the von Pirquet medal for outstanding achievement in allergy.

BOSTON HEALTH DEPARTMENT EXAMINATIONS FOR TUBERCULOSIS

Gastric examinations for tuberculosis may be obtained by appointment on Mondays, Wednesdays and Thursdays at the laboratory of the Boston Health Department, Haymarket Square (Telephone, CA 7-1300). Examinations may be obtained for their patients by all physicians, but the patients must live in Boston.

VETERANS ADMINISTRATION RESIDENCY TRAINING IN NEUROPSYCHIATRY

A limited number of openings are available for July 1, 1950, appointment to the Veterans Administration residency training program in neuropsychiatry. This program is under the jurisdiction of the deans of the Boston medical schools (Harvard, Tufts and Boston University). Training in this program, which may be from one to three years, is given at the following institutions:

Cushing Veterans Administration Hospital, Framingham, Massachusetts.

Bedford Veterans Administration Hospital, Bedford, Massachusetts.

The Mental Hygiene Clinic of Boston, Regional Office of Veterans Administration, Boston, Massachusetts.

West Roxbury Veterans Administration Hospital, West Roxbury, Massachusetts.

White River Junction Veterans Administration Hospital, White River Junction, Vermont.

Emphasis in the entire program is on psychiatry with dynamic orientation and includes closed-ward, open-ward, outpatient and child psychiatry and neurology. Training in child psychiatry is given at the Children's Medical Center, Massachusetts General Hospital and Hahn Clinic, Boston.

All stations are within commuting distance of the Boston Psychoanalytic Institute, in the event that applicants have been accepted for analytic training.

Further information may be obtained from: Dr. [Name], Chief, Professional Services, Bedford Veterans Administration Hospital, Bedford, Massachusetts; Dr. [Name], Chief, Neuropsychiatric Clinic, West Roxbury Veterans Administration Hospital, Framingham. (Notes concluded.)

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TO

The New England Journal of Medicine

Volume 241, July 7, 1949 to December 29, 1949

PAGES ACCORDING TO WEEKLY ISSUES

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KEY TO ABBREVIATIONS

bml — Boston Medical Library	me — notes from medical examiner	ness — New England Surgical Society
c — correspondence	mms — Massachusetts Medical Society	n — notice
cr — case record	mp — medical progress	o — obituary
e — editorial	misc — miscellany	o — original article
mdph — Massachusetts Department of Public Health	nepa — New England Postgraduate Assembly	

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CASE RECORDS
OF THE MASSACHUSETTS GENERAL HOSPITAL
WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

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